DOCTORAL THESIS

Antibiotic resistance: patient-clinician communication and decision-making about antibiotic use in primary care.

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Antibiotic resistance: patient-clinician communication and decision-making about antibiotic use in primary care

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Thesis abstract

Background— Antibiotics are inappropriately prescribed for many acute respiratory infections (ARIs) in primary care, for which they offer marginal benefits. This use of antibiotics is an important contribution to the worldwide problem of antibiotic resistance. Consultations between clinicians and patients with ARIs are well-suited for shared decision making (SDM) because of the antibiotic benefit-harm trade-off. However, little research has analysed the extent and nature of SDM in consultations in the context of ARIs, including what and how antibiotic benefits and harms are communicated. There is also limited research that has explored patients' understanding of antibiotic resistance, its consequences, or whether patients consider its threat when deciding whether to use antibiotics for ARIs.

Aims— This thesis aimed to explore: patient-clinician communication, including the use of SDM, of antibiotic benefits and harms (including antibiotic resistance as one of the harms during ARI consultations); patients' understanding of antibiotic resistance and aspects of it (such as resistance reversibility and resistance spread among family members); and how these influence patients' attitudes towards antibiotic use. Investigating these aims also required updating the current evidence about resistance development and decay by performing a systematic review.

Methods— Four interrelated studies were conducted. Study 1 was an observational study in Australian general practices, nested within an ongoing cluster randomised trial of patient decision aids. In this study, consultations were audio-recorded, and the extent and nature of SDM in consultations between general practitioners (GPs) and patients with ARIs were subsequently analysed. Antibiotic benefits and harms communication, with and without the use of patient decision aids, was also explored. Study 2 was a qualitative study which used semi-structured interviews to explore patients' understanding of antibiotic resistance, and related aspects, in a sub-sample of patients with ARIs who presented to GPs in Study 1. Study 3 was a systematic review and meta-analysis that examined the development and decay of antibiotic resistance in community patients after antibiotic use. This review was hampered by poor reporting, which

led to quantitative analysis (Study 4) that examined the quality of reporting of studies included in Study 3 using checklists developed from existing reporting guidelines.

Results— Study 1 analysed 36 GP-patient consultations and found the extent of observer-assessed SDM between GPs and patients with ARIs was generally low (mean (SD) total observing patient involvement in decision making (OPTION12) score= 29.4 (12.5; 100-point scale). When patient decision aids were used (n=15 consultations), a balanced discussion of antibiotic benefits and harms occurred more often and was more comprehensive, with antibiotic resistance mentioned in 10 (67%) of these consultations. When decision aids were not used (n=21), antibiotic harms were rarely mentioned (n=1, 5%) and antibiotic resistance was never mentioned.

Study 2 revealed five key themes about people's understanding and consideration of antibiotic resistance: 1) antibiotic use is seen as the main cause of resistance, but what it is that becomes resistant is poorly understood; 2) resistance is perceived as a future 'big problem' for the community, with little appreciation of the individual impact of, or contribution to it; 3) poor awareness that resistance can spread between family members, but concern that it can; 4) low awareness that resistance can decay with time and variable impact of this knowledge on attitudes towards future antibiotic use; and 5) antibiotics are perceived as sometimes necessary, with some awareness and consideration of their harms.

The systematic review (Study 3) included 25 studies (16,353 children and 1,461 adults). The review showed that antibiotic resistance in *Streptococcus pneumoniae* initially increased fourfold after penicillin-class antibiotic exposure, but fell after one month (OR 1.7, 95% CI 1.3–2.1). For cephalosporins, the odds of isolating resistant bacteria was lower than for penicillins directly after exposure, but after one month returned to similar odds as it did for the penicillins. Macrolides were also associated with increased antibiotic resistance immediately after use, which persisted for at least three months (OR 8.1, 95% CI 4.6–14.2, from controlled studies and OR 2.3, 95% CI 0.6–9.4, from time-series studies). Resistance in *Haemophilus influenzae* after penicillins was not significantly increased initially, but was at one month (OR 3.4, 95% CI 1.5–7.6), before falling

to insignificant levels by three months. Data at three months was sparse for cephalosporins and macrolides.

Study 4 showed varied reporting quality of studies included in the previous systematic review. The mean percentage (SD, range) of studies that adequately described all the checklist items was 59% for RCTs (14%, 36%–84%) and 52% for prospective cohort studies (17%, 13%–70%). Aspects of the studies, such as the sampling procedures used, and rationale for the study, were described in most studies, although specific details (such as about blinding, and the actual incidence of resistant and susceptible isolates analysed at each time-point) were missing in many.

Conclusions and Implications— These studies highlighted the potential benefits that would arise from an increase in the proportion of consultations between clinicians and patients with ARIs in which SDM occurs. A balanced discussion, including how resistance is a potential harm of antibiotics, and what the possible consequences of this are, but that resistance decays with time (even if faster than previously reported), might lead to better engagement with patients about antibiotics. Patient decision aids are one method of assisting in this. Overall, addressing this need may reduce patients' desire for, and use of, antibiotics for ARIs, but this needs empirically testing with further research. Moreover, research reporting antibiotic resistance needs to be improved at all levels from randomised trials to systematic reviews and other guiding documents. Establishing the need to consider the collection and aggregation of expert opinion to develop a globally endorsed reporting checklist for better reporting of antibiotic resistance in studies with prospective designs. Simultaneous measures to tackle antibiotic resistance, from communication to reporting, need to be implemented, to avoid living in a time when a simple prick injury could lead to death from an untreatable infection.

Keywords

Antibiotics, Antibiotic Resistance, Decision Making, Decision Support Techniques, Physician-Patient Relations, Primary Care, Respiratory Tract Infections, Resistance Decay

Declaration by candidate

This thesis is submitted to Bond University in fulfilment of the requirements of the degree of Doctor of Philosophy (PhD). This thesis represents my own original work towards this research degree and contains no material that has previously been submitted for a degree or diploma at this University or any other institution, except where due acknowledgement is made.

Mina Abdou Thabet Bakhit

Declaration of author contributions

Mina Bakhit is the sole author of Chapter 1 (General Introduction), Chapter 2 (Literature Review), and Chapter 8 (General Discussion). The remaining chapters (listed below) are multi-authored publications on which Mina Bakhit was the lead, with other contributors acknowledged below. The design, conception, and management of all studies; data collection and analysis; initial drafting and subsequent revisions of publications; as well as response to peer-reviewers was primarily driven by the PhD candidate. Co-authors generally provided assistance with study planning and design, interpretation of the data, and critical revision of the manuscript.

Co-authored publications

1- **Bakhit M**, Del Mar C, Gibson E, Hoffmann TC. Shared decision making and antibiotic benefit-harm conversations: an observational study of consultations between general practitioners and patients with acute respiratory infections. *BMC Family Practice*; 2018, **19**(1):165. doi: 10.1186/s12875-018-0854-y.

2- **Bakhit M**, Del Mar C, Gibson E, Hoffmann TC. Exploring patients' understanding of antibiotic resistance and how this may influence attitudes towards antibiotic use for acute respiratory infections: a qualitative study in Australian general practice. *BMJ Open* 2019;9:e026735. doi: 10.1136/bmjopen-2018-026735.

3- **Bakhit M**, Hoffmann TC, Scott AM, Beller E, Rathbone J, Del Mar C. Resistance decay in individuals after antibiotic exposure in primary care: a systematic review and meta-analysis. *BMC Medicine* 2018; **16**:126. doi: 10.1186/s12916-018-1109-4.

4- **Bakhit M**, Del Mar C, Scott AM, Hoffmann TC. An analysis of reporting quality of prospective studies examining community antibiotic use and resistance. *BMC Trials* 2018; **19**:656. doi: 10.1186/s13063-018-3040-6.

Statement of contributions

1. MB 70%, CDM 10%, EG 5%, TH 15%
2. MB 70%, CDM 10%, EG 5%, TH 15%
3. MB 65%, TH 10%, AMS 5%, EB 5%, JR 5%, CDM 10%
4. MB 70%, CDM 10%, AMS 5%, TH 15%

Research outputs arising from this thesis

Peer-reviewed publications

1- **Bakhit M**, Del Mar C, Gibson E, Hoffmann TC. Shared decision making and antibiotic benefit-harm conversations: an observational study of consultations between general practitioners and patients with acute respiratory infections. *BMC Family Practice*; 2018, **19**(1):165. doi: 10.1186/s12875-018-0854-y.

2- **Bakhit M**, Del Mar C, Gibson E, Hofmann TC. Exploring patients' understanding of antibiotic resistance and how this may influence attitudes towards antibiotic use for acute respiratory infections: a qualitative study in Australian general practice. *BMJ Open* 2019;9:e026735. doi: 10.1136/bmjopen-2018-026735.

3- **Bakhit M**, Hoffmann TC, Scott AM, Beller E, Rathbone J, Del Mar C. Resistance decay in individuals after antibiotic exposure in primary care: a systematic review and meta-analysis. *BMC Medicine* 2018; **16**:126. doi: 10.1186/s12916-018-1109-4.

4- **Bakhit M**, Del Mar C, Scott AM, Hoffmann TC. An analysis of reporting quality of prospective studies examining community antibiotic use and resistance. *BMC Trials* 2018; **19**:656. doi: 10.1186/s13063-018-3040-6.

Peer-reviewed conference abstracts: oral presentations

- **Bakhit M**, Hoffmann TC, Scott AM, Beller E, Rathbone J, Del Mar C. Resistance decay in individuals after antibiotic exposure in primary care: a systematic review and meta-analysis. National Medicines Symposium 2018: Canberra, Australia
- **Bakhit M**, Del Mar C, Gibson E, Hoffmann TC. Exploring patients' understanding of antibiotic resistance and its influence on attitudes towards antibiotic use for minor illnesses: a qualitative study. Bond University Higher Degree Research Conference 2018: Gold Coast, Australia (second place for best oral presentations)
- **Bakhit M**, Del Mar C, Gibson E, Hoffmann TC. Exploring patients' understanding of antibiotic resistance and its influence on attitudes

towards antibiotic use for minor illnesses: a qualitative study. Gold Coast Health Research Week Conference 2018: Gold Coast, Australia

Peer-reviewed conference abstracts: posters

- **Bakhit M**, Rathbone J, Del Mar C, Hoffmann TC. Does antibiotic use in primary care increases antimicrobial resistance in individuals? A systematic review. Bond University Higher Degree Research Conference 2016: Gold Coast, Australia (best poster by judges)
- **Bakhit M**, Del Mar C, Hoffmann TC. Analysis of the extent of shared decision making in consultations between Australian general practitioners and patients with acute respiratory infections. 9th International Shared Decision Making Conference 2017: Lyon, France

Other presentations

- **Bakhit M**. Is Bacterial Resistance Reversible? Three-Minute Thesis competition 2016: Bond University.

Media coverage

- **Bakhit M**. Interview with Ian Skippen 'Pop-Up Radio Australia'. National Medicines Symposium 2018. https://soundcloud.com/npsmedicinewise/nms2018-interview-with-mina-bakhit
- **Bakhit M**. Improving the conversation between doctors and patients about antibiotic benefits and harms for coughs and colds. *BMC Series blog*, October 2018. http://blogs.biomedcentral.com/bmcseriesblog/2018/10/17/improving-conversation-doctors-patients-antibiotic-benefits-harms-coughs-colds/

Ethics declaration

The research associated with Studies 1 and 2 of this thesis received ethics approval from the Bond University Human Research Ethics Committee. Approval number **0000015433**. Studies 3 and 4 did not require ethics approval.

Copyright declaration

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Abbreviations

Abbreviations included only in tables within the thesis are excluded from this list, as they are described in footnotes below each table.

ARIs:	Acute respiratory infections
AMS:	Antimicrobial stewardship
AOM:	Acute otitis media
ACEPP:	Assessing Communication about Evidence and Patient Preferences
aPR:	Adjusted prevalence ratio
BSIs:	Bloodstream infections
CI:	Confidence interval
CONSORT:	Consolidated Standards of Reporting Trials statement
COREQ:	Consolidated Criteria for Reporting Qualitative studies
CRP:	C-reactive protein
ESBL:	Extended spectrum β-lactamase
E. coli:	Escherichia coli
GPs:	General practitioners
GIT:	Gastrointestinal tract
GDP:	Gross domestic product
H. influenzae:	Haemophilus influenzae
MeSH:	Medical subject headings
MDRO:	Multi-drug resistant organisms
OR:	Odds ratio
OECD:	Economic Co-operation and Development
OPTION-12:	Observing Patient Involvement scale
PCT:	Procalcitonin
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta Analyses
RCT:	Randomised controlled trial
RR:	Risk ratio
ROBINS-I:	Risk of Bias in Non-Randomised Studies Interventions

S. pneumoniae:	Streptococcus pneumoniae
STROBE:	Strengthening the Reporting of Observational studies in Epidemiology
SDM:	Shared decision making
SD:	Standard deviation
TIDieR:	Template for Intervention Description and Replication
USA:	United States of America
WHO:	World Health Organisation

Chapter 1

General Introduction

"Mother, mother I am ill,
Send for the doctor from over the hill;
In comes the Doctor,
In comes the Nurse,
In comes the lady with
the alligator purse.
Penicillin says the Doctor,
Penicillin says the Nurse,
Penicillin says the lady with
the alligator purse."

-Lilliput magazine version of an old skipping song

Background

Antibiotic resistance occurs when bacteria become resistant to antibiotic treatment (1). The rise of antibiotic resistance means that effective and inexpensive antibiotic treatment for simple infections is being lost (2), leading us towards a post-antibiotic era (3). In the year 2050, 10 million people are expected to die as a direct result of antibiotic resistance, exceeding the number of people expected to die from cancer or road traffic accidents (4). This makes antibiotic resistance one of the world's most threatening public health crises.

Antibiotic use is the main driver of resistance (5-7). In healthcare, the inappropriate use of antibiotics, such as for conditions where there is minimal or no benefit from their use, is contributing to an increase in resistance rates (8). In Australia, over 30 million prescriptions for antimicrobials were dispensed in 2015 (9, 10). The majority of these were prescribed in primary care, and in this setting, the most common indication is for ARIs. Australian clinicians prescribe antibiotics for more than 60% of patients with acute respiratory infections (ARIs) (9).

There are common misperceptions about antibiotic use by both clinicians and patients. Clinicians often perceive that patients with ARIs who come to see them are expecting antibiotics (11, 12). Sometimes incorrectly, many patients overestimate the benefits of antibiotic treatment and underestimate the harms (13), believing that antibiotics provide benefit for all infections, including viral infections (14). These misperceptions are often not elicited, articulated or addressed in routine consultations.

If the volume of antibiotic use for ARIs in primary care can be reduced through better communication and discussion about antibiotics (and their benefits and harms during routine clinical consultations), the impact on individuals, health systems and wider communities would be considerable.

Aims

The core aim of this PhD is to explore patient-clinician communication of antibiotic benefits and harms for ARIs along with patients' understanding of antibiotic resistance, its aspects such as resistance decay and spread among people who live in close proximity and how these influence patients' attitudes towards antibiotic use. To fulfil this main aim, the following research questions, grouped into themes, were explored:

Research questions

Theme one: Patient-clinician communication about antibiotic treatment for ARIs

1) What is the extent and nature of shared decision making in consultations between GPs and patients with ARIs, including if and how antibiotic benefits and harms are discussed? Does the discussion about antibiotic harms include antibiotic resistance?
2) Are decision aids used in ARI consultations? Does the communication of antibiotic benefits and harms differ with and without the use of decision aids?
3) What are patients' perspectives of the decision-making process?

Theme two: Patients' understanding of aspects of antibiotic resistance and its influence on attitudes to antibiotic use

4) What is patients' understanding of antibiotic resistance directly after the decision-making point in a clinical encounter for ARI?
5) What is patients' understanding of antibiotic resistance aspects such as resistance decay and spread among people in close proximity? How have these influenced attitudes towards antibiotic use?

Theme three: Evidence about resistance development and decay, including the reporting quality of antibiotic resistance studies

6) What is the updated evidence about the development and time to resistance decay among community individuals following exposure to antibiotics?
7) Does the behaviour of resistance decay differ among the different type of bacteria and antibiotic classes?

8) What is the completeness of reporting of prospective primary studies that have examined antibiotic use and resistance?

Outline of the thesis

Research questions 1-8 are presented as four separate but interrelated studies, with each study representing one chapter within the overall thesis. Two of these studies (Chapters 3 and 5) comprise work already published in peer-reviewed journals, and two others (Chapters 4 and 6) represent studies which are currently under review. The published chapters and associated references, along with each study's supplementary materials, have been formatted consistently throughout the body of the thesis and the numbering of figures and tables kept continuous.

Chapter outline

Chapter 2 draws information from published trials, reviews, and other literature that have explored the problem of antibiotic resistance and its impact on the individual, community, and economy; antibiotic use and its communication in primary care; and the current evidence gaps in relevant antibiotic resistance research.

Chapter 3 (Study 1; Questions 1, 2 and 3) describes an observational study that analysed audio-recordings of consultations between GPs and patients with ARIs. The study was nested within an ongoing randomised controlled trial (RCT) of decision aids for the most common ARIs (acute bronchitis, sore throat, acute otitis media). The study explored the nature and extent of shared decision making during routine clinical consultations, including communication about antibiotic benefits and harms, and how this differed if and when, decision aids were used during the consultations.

Chapter 4 (Study 2; Questions 4 and 5) comprises a qualitative study conducted in a convenience sample of participants (recruited as part of Study 1) who had an ARI and were consulting a GP. The study explored patients' understanding of antibiotic resistance and its aspects of it (such as spread among people who live in close proximity and antibiotic resistance decay) and how knowledge about antibiotic resistance influenced attitudes towards antibiotic use.

Chapter 5 (Study 3; Questions 6 and 7) presents a systematic review and meta-analysis examining the development and decay of antibiotic resistance following individual exposure to antibiotics in primary care. Finally, Chapter 6 (Study 4; Question 8) describes an analysis of the reporting quality of antibiotic resistance among studies with prospective designs included in Study 3.

Chapter 7 draws together the findings and novel contributions of the four research studies, within the broader scope of the whole thesis aims. Further, the chapter also discusses the implications of these findings for clinical practice, policymakers and identifies where future research efforts should be focused.

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Chapter 2

Literature Review

"The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism."

-Sir Alexander Fleming

2.1 Antibiotic resistance

Antibiotics have been critically important for treating infections since their discovery in the 1940s. However, in recent years, antibiotics are accelerating towards weakened effectiveness due to an increase in antibiotic resistance (1). Antibiotic resistance occurs when bacteria change in response to using antibiotics by selection, or induction, of genes to code for proteins that inactivate the antibiotic molecule (2). Antibiotic resistance has been growing rapidly over the past few decades (1, 3). It has emerged in all known antibiotics, and no new antibiotics have been developed to alleviate the resistance crisis (4).

The emergence of antibiotic resistance

Bacteria level

Bacteria continuously evolve to resist antibiotics, as a direct result of the warfare between microbes (5, 6). Bacteria are selected to develop resistance mechanisms to overcome the action of the antimicrobial molecules within their environment (e.g. soil) (5, 6). This ‘intrinsic resistance’ describes the process by which genes that generate resistance already exist in the bacterial genome (7). These genes can be switched on by human, agricultural or animal use of antibiotics, or acquired either by mutation or gene transfer from another species of bacterium (so-called ‘acquired resistance’) (5, 6).

Individual human level

The human commensal microbiome consists of harmless bacteria present in body sites (e.g. the gastrointestinal tract (GIT) or skin). The microbiome is established as early as the first day in neonates (8). In the absence of selective pressure (e.g. antibiotic exposure), both resistant and susceptible bacteria co-exist in harmony (9). With post-selective pressure from antibiotic use, resistance occurs when naturally susceptible bacteria acquire the genes encoding the resistance mechanism via mutation or genetic transfer from other resistant bacteria (through the methods of conjugation, transduction, or transformation) (10). Thus, antibiotic use by an individual increases the risk of resistance expression (11, 12) and decreases the microbiome population of susceptible bacteria.

Population level

Millions of metric tonnes of antibiotics have been manufactured and utilised for a variety of human, animal, and agricultural uses, contributing significantly to antibiotic resistance selection (5-7). The link between antibiotic use and resistance is complex and incorporates multiple confounding factors (5, 13) including: 1) bacterial factors such as individual bacterial types, their mutation rates and pathogen host interaction; 2) human factors such as human-human transmission and vaccination; 3) and public health factors such as antibiotic resistance from food-producing animals, travel to high antibiotic-resistant destinations and sanitation (5).

The spread of antibiotic resistance

Antibiotic resistance can be spread by different means such as animal-human or human-human transfer (Fig. 1).

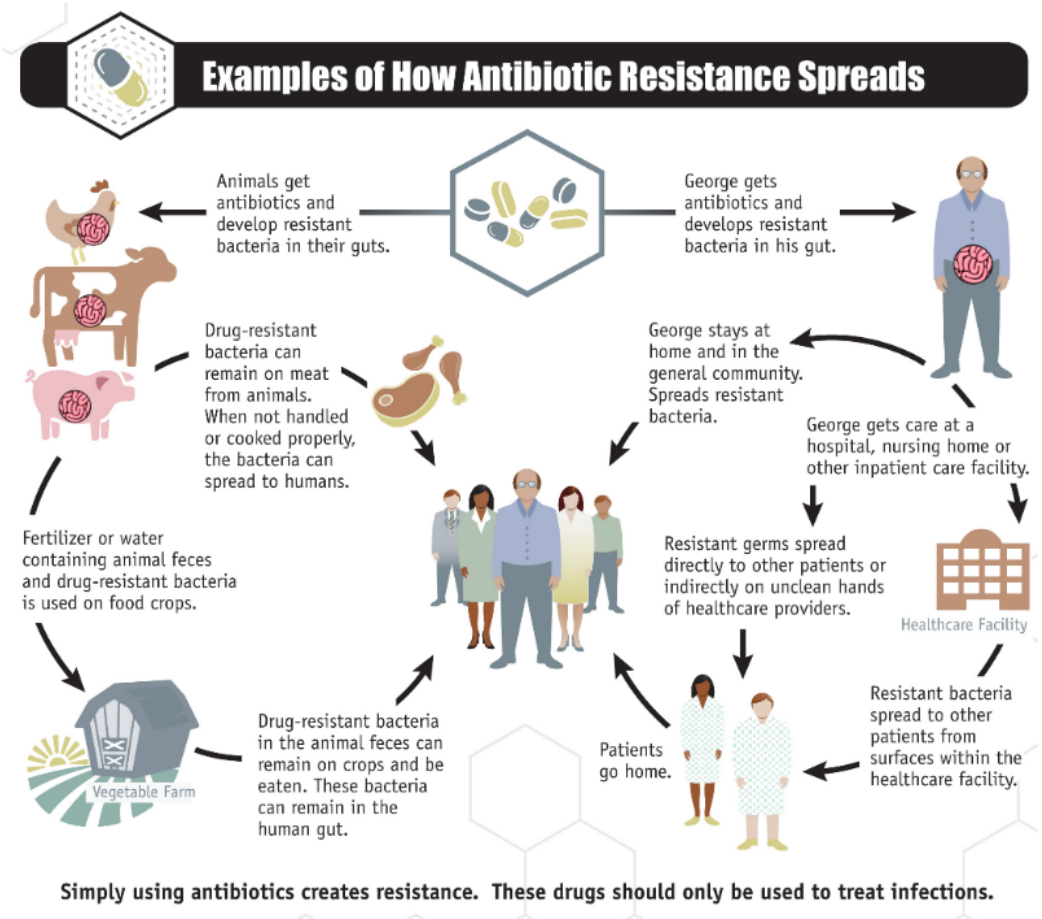


Fig. 1. The spread of antibiotic resistance (14)

Animal-human transfer

Giving antibiotics to animals kills many bacteria, leaving behind the resistant strains. Subsequently, animal-human transfer can occur through: 1) direct close human contact with farm animals (15) or animals in wildlife (16); 2) when food animals are slaughtered and processed, or from handling meat or other products contaminated with resistant bacteria (17); and 3) when irrigation water containing contaminated fertilisers or animal faeces is used on food crops (18).

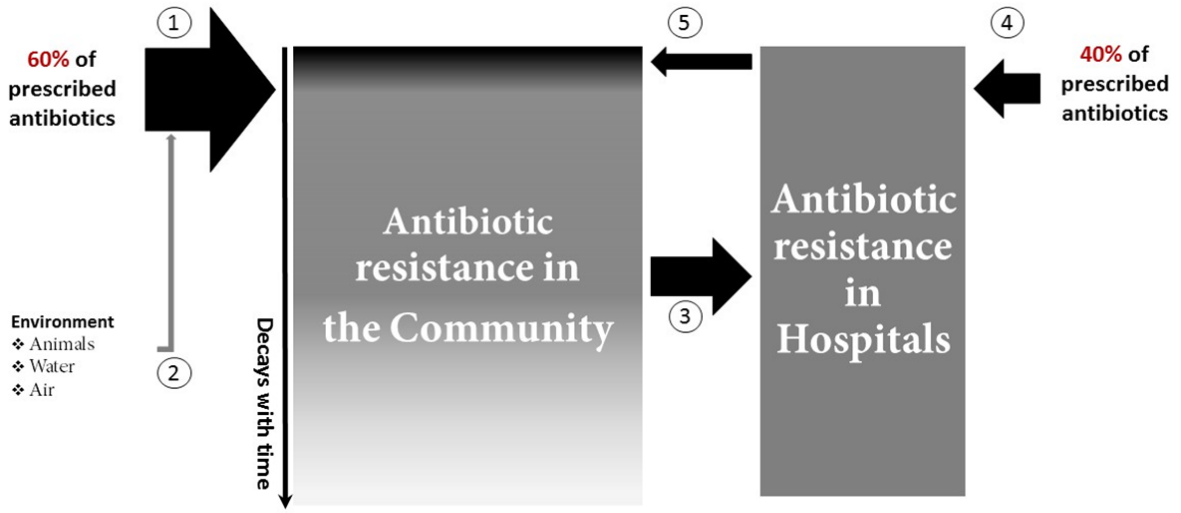
Human-human transfer

Antibiotic resistance can be spread between humans either by contact inside healthcare settings (19), or community settings (20).

Within hospitals, antibiotic resistant bacteria can transfer from one patient to another by healthcare workers with poor hand-hygiene practice, low hygiene/cleanliness of the hospital environment, or direct contact between hospitalised patients (19).

Within community individuals, a recent study showed that fluoroquinolone treatment for patients with suspected urinary tract infections led to a two-fold increase in ciprofloxacin-resistant *Enterobacteriaceae* and an associated increased individual risk of colonisation for other household members (adjusted prevalence ratio (aPR)=1.8, 95% Confidence Interval (CI) 1.3–2.5) (21). Transmission between individuals can also occur through interaction within community-based settings such as nursing homes, schools, day care centres, through community activities such as sports participation, and by travel to high antibiotic resistance destinations (20).

This continuous transfer cycle between hospitals and the community leads to the continuous load of antibiotic resistance at both ends. As most antibiotics are prescribed in the community, it is of paramount importance that efforts are directed towards reducing antibiotic use there (Fig. 2).



1,4. Individual antibiotic use lead to emergence of antibiotic resistance
2. Antibiotic resistance can be transferred from the environment to community individuals
3. Patients infected with community-acquired resistance strains get admitted to hospitals and contribute to the risk of transmission of resistant bacteria strains to hospital environment
5. Antibiotic resistance can be transferred from hospitals to the community through healthcare workers, discharged patients, or nursing home residents.

Fig. 2. Antibiotic resistance transfer cycle between hospitals and the community

The impact of antibiotic resistance

Antibiotic resistance has several negative impacts on individuals, healthcare systems, and the economy.

Impacts on morbidity and mortality

In the United States of America (USA) alone, the estimated number of infections caused by antibiotic resistance is about two million, coupled with 23,000 deaths each year (22). In the year 2050, 10 million people are expected to die as a direct result of resistance, exceeding the number of people expected to die from cancer or road traffic accidents (23).

Patients with infections caused by resistant bacteria experience up to a two-fold increased rate of adverse outcomes compared with similar infections caused by susceptible strains (24). These patients also require the use of more toxic antibiotics for their treatment (25).

Patients infected with resistant strains may often require additional surgical procedures such as revascularisation or debridement of the infected tissue (26)

and have a higher risk of complications (27), treatment failure, and transmission of infection to others (28).

A systematic review which compared mortality associated with methicillin-resistant (MRSA) and methicillin-susceptible Staphylococcus aureus bacteraemia found a significant increase in mortality associated with MRSA bacteraemia (Odds Ratio (OR)=1.93, 95% CI 1.52–2.42) (29). Similarly, strains of Enterobacter producing Extended Spectrum β-lactamase (ESBL) in patients with bacteraemia are associated with an increased risk of mortality (Risk Ratio (RR)=1.85, 95% CI 1.39–2.47), and increased incidence of delay in effective therapy (RR 5.56, 95% CI 2.94–10.51) (30).

Increased morbidity and the length of hospitalisation stays reflect the short-term effects of antibiotic resistance on affected patients. However, there are also longer-term consequences, including effects on patients' future health and possible isolation during future hospitalisation, and treatment with antibiotics, even if the patient's infection is not caused by resistant strains (for example, if a patient with previous MRSA infection, develops a fever though to be associated with a bacterial infection, they will be treated with vancomycin). Furthermore, other non-clinical effects, include loss of work and family time (due to prolonged hospitalisation), and the emotional impact correlated with having an infection with resistant bacteria (24).

Healthcare system impacts

The emergence and spread of antibiotic resistance from the community into hospitals threaten the safety and efficacy of many medical procedures. In hospitalised patients with any infection, antimicrobial susceptibility testing is not common before treatment (24). Consequently, a mismatch can occur between the initial therapeutic agent and subsequent results of susceptibility testing, leading to delay of effective treatment (24). In a case-control study comparing clinical outcomes of patients with pneumonia caused by resistant organisms and those with infections caused by susceptible organisms, those with infection caused by resistant organisms were treated with effective antibiotics at a median of 72 hours after infection was suspected whereas patients infected with

susceptible strains received appropriate antibiotics after a median of 11.5 hours (31).

Infection, or colonisation, with resistant strains has implications on the decision about the management of many common treatments, such as specific surgical procedures, implantable devices, and immunosuppressive therapy following transplantation operations. In the USA alone, it is estimated that between 38.7% and 50.9% of organisms which cause surgical site infections and 26.8% of organisms which cause infections after chemotherapy are resistant to standard antibiotics used for prophylaxis (32). For example, a 30% reduction in antibiotic prophylaxis efficacy in patients undergoing blood cancer chemotherapy, would cause an additional 683 deaths (32). Similarly, the same reduction in antibiotic prophylaxis efficacy in patients undergoing colorectal surgery, would cause an additional 4586 deaths (32).

Patients infected with resistant strains require additional nursing care, consumables (e.g. gloves), diagnostic tests and imaging, and intensive care unit and post-acute care bed occupancy (33). In a retrospective review of patients with ESBL *E. coli* bloodstream infections (BSIs), the cost of antibiotic therapy increased 1.6-fold (mean ± SD, EUR 763 ± 437 versus 474 ± 270 for non-ESBL BSIs; $p<0.001$), the cost of nursing care increased 1.9-fold (mean ± SD, EUR 3,894 ± 1,078 versus 2,001± 163 for non-ESBL BSIs; $p=0.03$), and the cost of other consumables (e.g. gloves) (mean ± SD, EUR 2,869 ± 2,676 versus 1,921 ± 2,152 for non-ESBL BSIs; $p= 0.02$) (34).

Economic impacts

A systematic review of the cost impact of antibiotic resistant infections in inpatient care found a threefold increase in hospital costs among patients who had infections with multi-drug resistant organisms (MDRO) compared to non-MDRO strains (35). In a study in a teaching hospital in the USA which measured the medical and societal cost attributable to antibiotic resistant infections, the mean cost difference between patients with antibiotic resistant infections and matched controls was up to US$29,069 per patient (36).

Antibiotic resistance is no longer limited to threatening individual health, as it poses huge economic costs if it remains unaddressed (23). In the USA alone, it

has been estimated that infections caused by antibiotic resistance cost the US health system US$20 billion, and US$35 billion in lost productivity, annually (22). By the year 2050, it is expected a cumulative cost to the global economic output of 100 trillion USD (23); or about 0.16% of the Gross Domestic Product (GDP) of all Organisation for Economic Co-operation and Development (OECD) countries (37).

Is antibiotic resistance reversible?

Antibiotic resistance can be reduced by decreasing antibiotic use. This is based on the assumption that a reduction in antibiotic use decreases selective pressure on resistance genes (5, 38, 39). However, the complexity of bacterial population dynamics and host-pathogen interaction make it difficult to predict resistance reversibility behaviour and time to decay.

Bacterial level

Two key factors explain the association between reduced antibiotic use and the reversibility or decay of antibiotic resistance: 1) the rate of appearance of resistant bacteria and the nature of resistance mechanisms and biological costs of resistance; and 2) the level of exposure to antibiotics and co-selection of resistance genes to more than one antibiotic (5, 38). Resistance traits are easily acquired by susceptible bacteria and may remain for some time without further exposure to antibiotic pressure (5). However, there is little empirical evidence about antibiotic resistance reversibility outside the laboratory in free living individuals.

Individual level

Resistance reversibility rates depend on bacterial factors besides individuals' microbiome health (normal bacterial flora) and the amount of antibiotic exposure (38). Studies of resistance decay in individuals were systematically reviewed in 2010 (12). The review found that resistant bacteria were detectable among commensals as long as 12 months after any antibiotic use, decaying exponentially from the maximum level directly after antibiotic use. However, there are methodological concerns with this review; specifically, the review combined data from prospective and retrospective studies. Using studies with retrospective

designs precludes the reporting of resistance at specific time points, which substantially reduces their contribution to estimating resistance decay. This suggests the current evidence should be updated, using synthesised evidence from only studies with prospective designs. Similarly, the rate of resistance decay between different bacteria, and following exposure to different antibiotic classes, have not been studied. Chapter 5 of this thesis reports on the findings from Study 3 that investigated this research gap.

This complexity of resistance reversibility makes a prediction about its decay at the bacterial level difficult. However, reducing antibiotic use by individuals will delay the emergence of antibiotic resistance and decrease the load of resistance within the community.

2.2 Antibiotic use in primary care

The alarm was raised as early as the discovery of penicillin that antibiotics could be overused when Sir Alexander Fleming (who discovered penicillin) himself pointed out that *"The time may come when penicillin can be bought by anyone in the shops."* (40). One major driver of antibiotic resistance is the high volume of antibiotic use (41-43). In healthcare, the inappropriate use of antibiotics, especially for conditions where there is no or minimal benefit from their use, is contributing to rapidly increasing resistance rates (44).

Australia's antibiotic use is high compared to countries with similar socioeconomic status (45). In Australia, over 30 million prescriptions for antimicrobials were dispensed in 2015 (46). The majority of these were prescribed in primary care (46) where ARIs account for 10% of consultations (47). Australian clinicians prescribe antibiotics for more than 60% of patients with an ARI (46). Evidence from systematic reviews concludes that antibiotics have minimal benefit for most patients presenting with a sore throat (48), for preventing recurrent sore throat (49), for acute otitis media (AOM) (50), sinusitis (51, 52), cold (53), bronchitis (54), or laryngitis (55).

In Australia, an estimated mean of 5.97 million (95% CI 5.69–6.24 million) cases of ARIs every year are managed in general practices using at least one antibiotic (56). If GPs adhered to the recommendations in Australian clinical practice guidelines (specifically for the management of AOM, acute pharyngitis or

tonsillitis, acute rhinosinusitis, and acute bronchitis/bronchiolitis), they would have prescribed antibiotics at 11–23% of the current prescribing rate (0.65-1.36 million ARI cases per year) (56). Given the high level of antibiotic prescribing for ARIs in Australian primary care, focusing on reducing this level of prescribing has been the target of several strategies and initiatives and is the focus of the research in this thesis (56).

The factors influencing antibiotic prescribing behaviour

There are patient and clinician-related factors that influence clinicians' antibiotic prescribing behaviour.

Patient-related factors

Many patients believe that antibiotics provide benefits for all infections, including viral infections (57, 58). In a systematic review which explored public knowledge and attitudes about antibiotics, 53.9% (95% CI 41.6–66.0%) of patients did not know that antibiotics cannot treat viral infections and 49.7% (95% CI 39.6–59.8%) did not know that antibiotics are not useful for flu and cold (59).

Across nearly all medical treatments and tests, patients tend to overestimate the benefits and underestimate the harms (60). In a cross-sectional study of Australian parents (or caregivers) of children aged 1 ≤ 12 years, about their knowledge and expectations of antibiotic benefits and harms for ARIs, most parents (or caregivers) overestimated antibiotic benefits (61). Many participants believed that complications are less likely with antibiotic treatment and that antibiotics greatly reduce the length of the illness (e.g. 5.4 days mean reduction in acute cough compared to evidence-based estimates of <0.5 days). This contributes to both patients' and parents' expectations and requests of antibiotics for ARIs.

Patients with ARIs are mostly seeking reassurance and information regarding their illness from their clinician (62, 63). In a survey of 1160 patients with ARIs visiting their GPs in the Netherlands, for patients who did not expect antibiotics, receiving reassurance was the only independent determinant of satisfaction (Adjusted OR 21.6, 95% CI 7.4–62.7). For patients who expected antibiotic

treatment, receiving reassurance (adjusted ORs of 4.7; 95% CI 1.9–11.9) was as important as being prescribed antibiotics (3.8; 95% CI 1.9–7.5) (62).

Clinician-related factors

Clinicians are the target for many interventions to reduce antibiotic prescribing; therefore, much research has investigated the factors that influence clinicians' antibiotic prescribing (64). A summary of these is presented here.

Clinicians' clinical knowledge: Several studies have looked at the relationship between clinical knowledge and antibiotic overprescribing. In a systematic review exploring GPs' antibiotic prescribing behaviours, 11 studies (31%) reported that clinicians' indifference to learning more about reducing antibiotic prescribing in ARI management was directly related to antibiotic overprescribing (65).

Diagnostic uncertainty and fear of disease progression: Clinicians with uncertainty about the diagnosis tend to prescribe more antibiotics to avoid missing treatable conditions 'just in case' and to avoid complications of bacterial illnesses (66-68). Patients' clinical features also influence diagnostic uncertainty. A cross-sectional study of paediatricians and family practitioners found that clinicians were nearly seven times more likely to prescribe antibiotics if their patients looked unwell and twice as likely if the child had a fever above 38.5°C (69).

Patients' perceived demand for antibiotics: Clinicians are almost three times more likely to prescribe antibiotics for their patients if they believe patients expect them (70). In a recent systematic review, clinicians reported patient (or parent) pressure as a major influence on their antibiotic prescribing behaviour (67). Some clinicians feel prescribing antibiotics strengthens their therapeutic relationship with the patient (71) and sometimes do so to avoid confrontation (72). However, patients' expectations are often misperceived by clinicians as many patients are more concerned about symptom relief and want treatment to alleviate the pain (63).

Time pressure: Being busy can influence GPs to provide antibiotics, as some GPs see this as a fast way of establishing a sense of security, patient satisfaction and concluding the consultation rapidly (73, 74).

Strategies to reduce antibiotic prescribing in primary care

This section presents some evidence-based strategies developed to reduce antibiotic prescribing, with emphasis on strategies which focus on improving the appropriateness of antibiotic prescribing for ARI management.

Public-targeted strategies

Nationwide mass media campaigns provide an opportunity to educate patients and the public about the aggravating crisis of antibiotic resistance and how they can help to reduce the severity of it. Several campaigns, consisting of extensive information dissemination across multiple channels, have been used in high-income countries to promote appropriate antibiotic use. Some of these, as examined in observational studies, have led to a significant reduction in antibiotic use. For example, after nationwide mass media campaigns, antibiotic use declined by 26.5% in France between 2002-2007 (75) and by 36% in Belgium between 1999-2000 and 2006-2007 (76). The success of public campaigns partially depends on the availability of funding to deliver the message and needed are robust data collection methods to evaluate the outcome measures of each campaign (77). However, these campaigns have been very costly incurring expenses in the tens of millions of dollars.

Clinician-targeted strategies

Two main ways to target clinicians' diagnostic uncertainty are by using diagnostic tests at point-of-care or through delayed prescribing.

Point-of-care diagnostic tests

Diagnostic tests within consultations may help clinicians to confirm the presence or absence of pathogenic bacteria causing the illness. Inflammatory cytokines trigger biomarkers of bacterial infection following tissue injury due to infectious (e.g. bacterial) and non-infectious conditions (e.g. trauma). With an increase in tissue damage or inflammation as a result of infection, the level of biomarkers in the blood increases. Test results can guide clinicians to the severity of the condition and allow them to identify which patients may benefit from antibiotic treatment and thus reduce unnecessary prescribing (78, 79). The two main point-

of-care biomarkers of infection tests are C-reactive protein (CRP) and procalcitonin (PCT) (80, 81).

A systematic review of the effectiveness of point-of-care CRP testing and antibiotic prescribing (82), found the testing significantly decreased antibiotic prescribing at index consultations (RR 0.78, 95% CI 0.66–0.92). Qualitative studies of clinicians' attitudes towards and experience of CRP tests, reported positive attitudes by clinicians regarding the quick availability of the test results. Clinicians were also empowered to prescribe fewer antibiotics than they perceived necessary and their confidence with their antibiotic prescribing decisions increased (83, 84). In a qualitative study nested within a RCT of CRP testing and clinician training in communication skills, patients were satisfied with their treatment decision, despite not receiving antibiotics. Further, most patients described the CRP test as something that could distinguish between a virus and a bacterium and help indicate when antibiotics are needed (85).

However, there are several challenges to the routine implementation of CRP testing in general practice. The reduction in antibiotic prescribing remains uncertain, and the test should be used as an adjunct to clinical examination, not as a substitute for it (82). In addition, CRP devices cost around AUD$1800-3000 plus consumable costs per test, which creates a challenge for private general practices in Australia with no reimbursement for this investment (86). Additionally, education on the use of the test may be needed to avoid the unintended consequence of antibiotic overprescribing (87).

Procalcitonin testing, as a biomarker of infection test, may help clinicians to decide when to initiate antibiotic treatment and when to stop it, reducing unnecessary antibiotic prescribing and decreasing the duration of antibiotic treatment (88). In a recent systematic review of the efficacy of using procalcitonin with patients with ARIs (89), procalcitonin guidance was associated with a 2.4-day reduction in total antibiotic exposure (mean 8.1 days in the intervention group, compared to 5.7 days in the control group, 95% CI -2.71– -2.15, $p< 0.001$).

Other candidates for point of care tests include white cell counts and anti-ASOT tests for streptococcal sore throat.

Delayed prescribing

The concept of delayed prescribing is to provide patients with an antibiotic prescription along with the suggestion to wait a few days before dispensing and only if the patient does not get better or the course of illness deviates from the expected (90). In a Cochrane systematic review that evaluated delayed prescription of antibiotics versus no or immediate antibiotics for patients with ARIs (91), delayed prescribing reduced antibiotic use compared to immediate antibiotic use by approximately 62% (31% versus 93%), with no differences in complication rate. Patients who received a delayed prescription were more satisfied over those who received no antibiotics (OR 1.49, 95% CI 1.08–2.06). Clinicians may use this strategy to help overcome prescribing antibiotics for fear of disease progression and its complications. This is midway between providing immediate antibiotics and no antibiotics at all (92).

Unfortunately, delayed prescribing is not widely used in general practices in Australia(92). The reasons are not clear why, but its implementation likely varies in different healthcare systems. Perhaps clinicians paid by fee-for-service (as in Australia) may have concerns about loss of income from not offering antibiotics immediately (93), although no research has investigated this. Another possible concern maybe the therapeutic vacuum left by not prescribing antibiotics. Patients may fill this vacuum with over-the-counter drugs, or complementary and alternative medicines (94). Although these products are not contributing to the resistance problem, they are mostly ineffective.

Patient-clinician communication strategies

Another strategy to reduce antibiotic use is to target patient-clinician communication within consultations. This addresses clinicians' perceptions that patients expect antibiotics and tend to overestimate their benefits. Therefore, encouraging clinicians and patients to discuss the benefits and harms of antibiotics, the option of not treating with antibiotics, and the patient's concerns and expectations may help patients to make an informed decision. Consequently, this may reduce inappropriate antibiotic prescribing in primary care.

Shared decision making

One strategy which shows promise for reducing antibiotic use is shared decision making (SDM). SDM is a process that involves clinicians and patients jointly participating in making a health decision. The decision-making occurs after the clinician and patient have discussed the options, the benefits and harms of each option, and considered the patient's values, preferences and circumstances (95, 96). It is part of a patient-centred model of consultation where there is two-way information exchange channel between experts; the patient is an expert in his or her illness and values, and the clinician is an expert in disease diagnosis and providing appropriate treatment (97). Patients' involvement in decision making can cause an increase in their satisfaction with the treatment decision, improved knowledge about benefits and harms of the available treatment options, a reduction in decisional conflict, and an opportunity to incorporate their values and preferences into clinical decisions (98, 99).

Despite the benefits of SDM, there are several misconceptions about it and challenges to its implementation in practice. It is commonly believed that participation in SDM will lead to longer consultations, despite a recent systematic review showing no increase in consultation duration when SDM occurred (100). Another is clinicians' perceived assumption that patients do not want, or are not able, to participate in making clinical decisions. This assumption was explored in several studies and systematically reviewed in 2012, where researchers found that in 71% of the studies conducted in or after 2000, most patients preferred sharing decisions with physicians (101).

SDM can be facilitated by using decision support tools. These tools can take several formats such as decision aids, option grids, decision boxes, question prompt lists or evidence summaries (98). A Cochrane systematic review of the effects of decision aids for people facing treatment or screening decisions, found that patients exposed to decision aids had higher knowledge scores compared to those who received usual care (mean difference= 13.27/100; 95% CI 11.32–15.23) and were more likely to have accurate risk perceptions (RR= 2.10; 95% CI 1.66–2.66) (99).

Shared decision making and antibiotic prescribing

Consultations for ARIs are especially suitable for shared decision making, because of 1) people's misperceptions of the need for and benefits of antibiotics and their underestimation of harms (61); 2) the delicate balance between benefits and harms, as there are marginal benefits and harms of antibiotics for ARIs; and 3) the tendency of some GPs to avoid exploring and managing patients' expectations about antibiotics. One method of executing this is to use "running commentaries" to set out these benefits and harms (102).

A systematic review found that interventions which facilitated SDM for consultations with patients with ARIs in primary care (103), significantly reduced short-term antibiotic prescribing, at or immediately after, the index consultation (47% in intervention groups to 29% in usual care; RR= 0.61, 95% CI 0.55–0.68; p< 0.001). This reduction in prescribing occurred without an increase in re-consultation rates (RR= 0.87, 95% CI 0.74–1.03) or decrease in patients' satisfaction (RR= 0.86, 95% CI 0.57–1.30). However, a long-term reduction in antibiotic prescribing for ARIs was not significantly reduced (RR= 0.74, 95% CI 0.49–1.11; p= 0.14).

Our research team has developed brief decision aids which target three common ARIs (sore throat, acute bronchitis, and acute otitis media) seen in general practice (See Supplementary Materials 1-3 published with Study 1 Chapter 3). The effectiveness of these decision aids was evaluated in a RCT with parents of children aged 1-16 years in a hypothetical illness scenario (104). More parents who received a decision aid made an informed choice (57%) compared with those who received standard written information (29%) (mean difference 28%, 95% CI 11%–45%, p< 0.01) and had higher total knowledge (mean difference 2.8, 95% CI 2.2–3.5, p< 0.01; 10-item scale) (104). However, this study used a hypothetical illness, and, therefore, the effect in real ARI consultations needs to be evaluated. To this end, a cluster randomised trial is underway in Australia to determine whether compared to usual care, these decision aids and a brief training package for the GPs (a 15-minute video explaining SDM and modelling how to use a decision aid) reduce GPs' antibiotic dispensing rate (Australian New Zealand Clinical Trials Registry (ANZCTR) number: ACTRN12616000644460) (105).

To improve the appropriateness of antibiotic prescribing, an in-depth understanding of the extent and nature of SDM within ARI consultations is important, including if and how antibiotic benefits and harms are discussed, whether decision aids are used, and if so, whether they are integrated within clinical encounters. Although antibiotic resistance is one harm of using antibiotics, it is an 'unusual harm' as it does not affect individuals during their current illness (but may affect the course of treatments for their future illnesses of the same or other infections). Moreover, it has additional societal harms with the potential transmission of antibiotic resistance to other community individuals. It is unknown if and how antibiotic resistance is discussed during routine consultations, and how that impacts on clinicians' discussion of antibiotic resistance, and patients' reaction to the problem.

Use of alternatives to antibiotics

Antibiotic treatment is poor at relieving the symptoms which accompany ARIs (such as fever, pain, cough). Wanting relief from these symptoms is the most common reason for patients with ARIs to visit their clinician (63). A RCT to evaluate the effectiveness of a standardised and evidence-based educational seminar for GPs about antibiotic prescribing found that the more drugs used for symptomatic treatment, the fewer antibiotics were prescribed by GPs (106).

In a survey of Australian parents, 63% of the sample reported using alternative treatments other than antibiotics for ARIs including analgesics, herbals, antihistamines, vitamins, honey, lozenges (61). The most commonly used over-the-counter symptomatic treatments were analgesics and antipyretics (e.g. acetaminophen, ibuprofen). For most of the other reported alternative treatments, there is insufficient evidence to properly know their efficacy with symptomatic treatment for ARIs such as vitamin C (107, 108), honey (109), probiotics (110), steroids (111-113), or zinc (114). Further investigations are needed in large randomised trials to test these alternative treatments.

Exploring understanding of antibiotic resistance to inform patient-clinician communication in primary care consultations

Understanding patients' and clinicians' knowledge and beliefs about antibiotic resistance, and reasons for using and not using antibiotics, can help inform interventions and public campaigns that aim to encourage appropriate antibiotic use.

Patients' knowledge and beliefs about antibiotic resistance

Patients generally believe that they are at low risk from antibiotic resistance in the community (115). The reasons may be partially explained by not viewing antibiotic resistance as a direct harm from antibiotic use. In Australia, a recent cross-sectional study found that 49% of the 401 participants reported antibiotic resistance as one of the potential harms of using antibiotics (61), but the reasons were not explored (this was a survey). This area needs further research.

Synthesised research that has explored the public's understanding of resistance (54 studies with 55,225 participants) (115) showed that: 1) the public have misunderstandings about antibiotic resistance (e.g., they were confused by whether antibiotic resistance was a function of the bacteria or host), 2) many participants believed they do not contribute to the development of resistance and that others cause it, and 3) they believe they are at low risk from resistance and it will not affect them personally. The systematic review identified knowledge gaps in the literature (115). First, there were no studies which explored if people knew that antibiotic resistance is reversible, the timelines of this, and its impact on attitudes towards antibiotic use. Nor were there studies that explored patients' knowledge of antibiotic resistance at the point of decision-making (instead, data came from hypothetical questions posed to healthy members of the public). These gaps are addressed in Study 2 (Chapter 4) of this thesis, in the context of antibiotic use for ARIs.

Clinicians' knowledge and beliefs about antibiotic resistance

A systematic review which explored clinicians' knowledge and beliefs about antibiotic resistance (57 studies, 11,593 clinicians) (116), found that many clinicians: 1) acknowledged the problem of antibiotic resistance, believing it was

a serious problem and that prescribing many antibiotics was the main cause (12); and 2) believed others, not themselves, caused the problem of antibiotic resistance, (other healthcare professionals or even patients), and several patient-related factors contribute to antibiotic resistance (such as using antibiotics for a shorter duration than prescribed, or non-adherence).

Antibiotic prescribing is influenced by clinicians' knowledge and beliefs about antibiotic resistance. A systematic review which explored clinicians' perceptions of factors influencing antibiotic prescribing, identified that clinicians' misperceptions about the relationship between overprescribing and antibiotic resistance were a major factor influencing antibiotic prescribing, and they did not believe that their antibiotic prescribing was causing antibiotic resistance and that it is caused by others (65). One suggested solution is to link clinicians' prescribing rates with local antibiotic resistance rates to demonstrate the causal relationship (117).

2.3 Evidence gaps in antibiotic resistance research and its communication in primary care

In 2015, the WHO launched a global action plan containing five strategic objectives: "1) to improve awareness and understanding of antimicrobial resistance; 2) to strengthen knowledge through surveillance and research; 3) to reduce the incidence of infection; 4) to optimise the use of antimicrobial agents; and 5) to ensure sustainable investment in countering antimicrobial resistance." (118).

Aligned with the strategic objectives of the WHO global action plan, particularly objectives one and four, this PhD aims to explore optimal communication of antibiotic resistance in primary care, with a focus on how antibiotic resistance and use are discussed within consultations between GPs and implications for decision-making.

Patient-clinician communication about antibiotic treatment for ARIs

As discussed earlier in this chapter, SDM is an effective strategy to reduce antibiotic prescribing for ARIs in primary care, but its uptake is low (103). This might be because adopting SDM in trials has been slow, extensive and

expensive. This may be a barrier to research translation. One strategy to facilitate SDM implementation within consultations may be using patient decision aids (99), because they are easier to implement in clinical practice. There has been little exploration of SDM in GP consultations for ARIs and whether and how antibiotic resistance is discussed during consultations. It is also unclear if patient decision aids, when provided, are used by GPs with patients with ARIs during their consultations and if their use influences discussion about resistance. These gaps are explored in Study 1 (**Chapter 3)**.

Patients' understanding of aspects of antibiotic resistance and its influence on attitudes to antibiotic use

Understanding patients' beliefs about antibiotics can help to inform interventions and public health campaigns which encourage appropriate antibiotic use. Little research has explored patients' understanding of resistance, the consequences of this, and whether patients consider the threat of resistance when deciding whether to use antibiotics. Perhaps, if people knew that antibiotic resistance is reversible, and it can be spread between those in close proximity (such as family members or households), this would influence their beliefs about, or use of antibiotics. These gaps are explored in Study 2 (**Chapter 4)**.

Evidence about resistance development and decay

Several RCTs provide evidence that resistance is reversible, and that bacterial susceptibility returns to the pre-antibiotic exposure levels after almost one month post penicillin-class antibiotic exposure (119) and six months post macrolide-class exposure (120). Studies reporting resistance decay following antibiotic exposure in the community were synthesised by one systematic review in 2010 (12). However, as discussed earlier, a systematic review of these studies (that includes retrospective designs) may be flawed. This prompted a need to synthesise the evidence of resistance decay with an up-to-date review, using evidence from studies with only prospective designs, to explore whether the rate of resistance decay varies between the different antibiotic classes and bacteria. These gaps are further explored in Study 3 (**Chapter 5)**.

The reporting quality of antibiotic resistance studies

High-quality reporting of the trials which have investigated antibiotic resistance is needed to conduct accurate systematic reviews. While conducting Study 3, common issues with antibiotic resistance reporting in the prospective studies became apparent. Hence, Study 4 (**Chapter 6)** was conducted to analyse and characterise the reporting problems so steps towards improving this in future studies can be taken.

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Chapter 3

Theme 1: Patient-clinician communication about antibiotic treatment for ARIs

Shared decision making and antibiotic benefit-harm conversations: an observational study of consultations between general practitioners and patients with acute respiratory infections.

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Preamble

Despite growing acknowledgment of the need for shared decision making and its role in reducing antibiotic prescribing for ARIs, there has been little exploration if and how it occurs in GP consultations for ARIs. To improve communication about antibiotic benefits and harms, there is a need to know what happens during routine consultations and if decision aids, when provided, are a useful tool for improving the conversation.

This chapter presents Study 1 which was published as an article entitled *"Shared decision making and antibiotic benefit-harm conversations: an observational study of consultations between general practitioners and patients with acute respiratory infections"*.

Work arising from this chapter was featured in BMC series blog network October 18, 2018, link: http://tinyurl.com/y8btr3ol, and was also presented as a poster at the 9th International Shared Decision Making Conference in Lyon, France between July 2nd and July 5th, 2017.

Abstract

Background — Little research has examined whether shared decision making (SDM) occurs in consultations for acute respiratory infections (ARIs), including what, and how, antibiotic benefits and harms are discussed. We aimed to analyse the extent and nature of SDM in consultations between GPs and patients with ARIs, and explore communication with and without the use of patient decision aids.

Methods — This was an observational study in Australian general practices, nested within a cluster randomised trial of decision aids (for acute otitis media [AOM], sore throat, acute bronchitis) designed for general practitioners (GPs) to use with patients, compared with usual care (no decision aids). Audio-recordings of consultations of a convenience sample of consenting patients seeing a GP for an ARI were independently analysed by two raters using the OPTION-12 (observing patient involvement in decision making) scale (maximum score of 100) and 5 items (about communicating evidence) from the Assessing Communication about Evidence and Patient Preferences (ACEPP) tool (maximum score of 5). Patients also self-completed a questionnaire post-consultation that contained items from CollaboRATE-5 (perceptions of involvement in the decision-making process), a decisional conflict scale, and a decision self-efficacy scale. Descriptive statistics were calculated for each measure.

Results — Thirty-six consultations, involving 13 GPs, were recorded (20 for bronchitis, 10 sore throat, 6 AOM). The mean (SD) total OPTION-12 score was 29.4 (12.5; range 4-54), with item 12 (need to review decision) the highest (mean=3) and item 10 (eliciting patients' preferred level of decision-making involvement) the lowest (mean=0.1). The mean (SD) total ACEPP score was 2 (1.6), with the item about discussing benefits scoring highest. In consultations where a decision aid was used (15, 42%), compared to the 21 usual care consultations, mean observer-assessed SDM scores (OPTION-12, ACEPP scores) were higher and antibiotic harms mentioned in all (compared to only 1) consultations. Patients generally reported high decision involvement and self-efficacy, and low decisional conflict.

Conclusions — The extent of observer-assessed SDM between GPs and patients with ARIs was generally low. Balanced discussion of antibiotic benefits and harms occurred more often when decision aids were used.

Keywords— Decision Making, General Practice, Respiratory Tract Infections, Decision Support Techniques, Physician-Patient Relations

Background

One of the main causes of increased antibiotic resistance is high levels of antibiotic use, with approximately 80% of antibiotic use occurring in the community (1). Within primary care, acute respiratory infections (ARIs) are one of the most common reasons for an antibiotic prescription, even though antibiotics provide only small benefit and can cause harms (2-5).

General practitioners' (GP) antibiotic prescribing behaviours are influenced by many factors, including diagnostic uncertainty, perceived patient pressure for antibiotics, and the need to maintain a good relationship with patients (6-9). Many patients believe that antibiotics resolve symptoms, are necessary, and have no harms (10). These beliefs contribute to some patients expecting, and sometimes requesting, antibiotics (10-12).

Shared decision making (SDM) is a process that involves clinicians and patients jointly participating in making a health decision, after having discussed the options and the benefits and harms of each option, and considered the patient's values, preferences and circumstances (13-15). For most ARIs, the choice about whether to treat with antibiotics, or not, is nearly at equipoise, with the benefits closely balanced by the harms. This makes consultations for ARIs ideally suited for SDM. When deciding about antibiotic use for ARIs, most patients want more involvement in the decision-making process and more opportunity to weigh up the benefits and harms of the options (16, 17). A recent systematic review found that interventions to facilitate SDM reduced antibiotic prescribing for ARIs in primary care, compared with usual care, from 47% to 29% (risk ratio of 0.61; 95% confidence interval 0.55 to 0.68) (18). However, there has been little exploration of the prevalence and nature of SDM in GP consultations for ARIs, including whether and how any patient decision aids may be used to facilitate SDM.

In a sample of consultations (where some GPs had been provided with ARI decision aids), we aimed to: 1) analyse the extent and nature of SDM in consultations between GPs and patients with ARIs, including if and how antibiotic benefits and harms are discussed; 2) explore the use of patient decision aids in ARI consultations and the communication of antibiotic benefits and harms with

and without decision aids; and 3) explore patients' perspectives of the decision-making process.

Methods

Design

This was an observational study that ran in parallel to an ongoing cluster randomised trial of three decision aids (for acute otitis media [AOM], acute sore throat, and acute bronchitis) and a brief GP SDM training package (19) (Australian New Zealand Clinical Trials Registry (ANZCTR) number: ACTRN12616000644460)

Participants and setting

For the trial, general practices were recruited from established GP research networks, primarily in southeast Queensland, Australia. Practices whose GPs had already consented for the trial or its pilot were invited to participate in, and provide written consent for, this additional study during 2017 (see Appendix 1 for GPs' consent form and information sheet). Practices were not eligible if they had participated in any other study where the main intention was to reduce antibiotic prescribing for ARIs. Patients were eligible to participate if they met the following criteria: 1) adult or parent of a child consulting a GP with one of three ARIs (AOM, acute sore throat, acute bronchitis) for the first time for that illness episode; 2) able to understand and read English; and 3) provided written informed consent (see Appendix 2 for patients' consent form and information sheet).

Some GPs (in practices that had been randomised to the trial's intervention group or had piloted the intervention) had previously been provided with: 1) three decision aids (one each for AOM, acute sore throat, and acute bronchitis), in printed form (single A4 page, double-sided and laminated) and in PDF (Supplementary Materials 1-3); and 2) a USB-drive containing a 15-minute video-based SDM training package that explained what SDM is, its use in ARI consultations, and a consultation demonstrating use of one of the decision aids. These GPs were given the intervention package and encouraged to use the aids during consultations with patients with ARIs whenever they felt it was appropriate. No further instruction or encouragement to use the aids or SDM strategies

occurred. The GPs in practices randomised to the control group did not receive the training package or decision aids and continued providing their usual care.

Procedure

The exact procedure for recruiting patients varied according to each practice's preference. On recruitment days, at some practices, one of us (MB) approached only patients who were waiting to see the GPs who were participating. In other practices, all waiting patients were approached and asked if they were waiting to see one of the participating GPs (GP names were listed). If so, we proceeded with recruitment. Patient eligibility was determined by asking the patients if they were suffering from one of the following symptoms (sore throat, cough, ear pain), and confirmed afterwards by the clinician. If the patient was diagnosed as having an illness other than an eligible ARI, the recording was deleted. After written informed consent was provided, an audio-recording device was handed to the GP who began recording just before the patient entered their consulting room. After patients left the room, they were given a short questionnaire (<5 minutes) to complete (see Appendix 3 for patient questionnaire). It contained basic demographic questions and items from tools to measure their perspectives of involvement in the decision-making process, decisional conflict, and confidence in decision-making (see section below on patients' perspectives).

Outcome measures

The extent of SDM (observer-assessed): Each consultation recording was analysed, by listening to the audio-recordings, by two independent raters using two measures. One measure was the 12-item Observing Patient Involvement (OPTION-12) scale, which has good discriminative validity, concurrent validity, and interrater and intra-rater reliability (20, 21). It contains 12 items scored on a five-point scale: (0) the behaviour was not observed; (1) a minimal attempt is made; (2) the behaviour is observed with a minimal skill level; (3) the behaviour is executed to a good standard; and (4) the behaviour is executed to a high standard. Total scores were re-scaled to 0-100. A second measure was 5 items (1 subscale) of the Assessing Communication about Evidence and Patient Preferences (ACEPP) tool. This was used as the OPTION scale does not specifically evaluate communication of the quantitative benefits and harms of the

options. It has good reliability and has been used previously to assess evidence communication in consultations (22, 23). The items rate clinicians' performance in describing the benefits/harms in terms of patient outcomes, the likelihood of benefits/harms, and the evidence source. Items were scored as: the behaviour was not observed (0); behaviour was observed at a basic level (0.5); or observed to an extended level (1).

To establish scoring reliability, three of us (MB, EG, TH) independently rated an initial sample of recordings and responses were discussed until agreement was reached. Two of us (MB, EG) independently rated the remainder. Any rating discrepancies were resolved by a third person (TH). The two raters also extracted verbatim any mention of antibiotic benefits and harms.

Patients' perspectives: Patients' perceptions of their involvement in the decision-making process were measured using the CollaboRATE-5 scale (score range 0 to 5) (24, 25). It asks three questions about what occurred in the consultation: 1) deliberation of the health issue, 2) exploration of patient preferences, and 3) integration of patient preferences (25). The scale has demonstrated significant discriminative validity, excellent intra-rater reliability and concurrent validity with other measures of SDM (24).

Decisional conflict is a condition of uncertainty about options involving trade-offs and potential for regret. It was measured using the 10-item low literacy decisional conflict scale (26). In this study, patients' feelings conflict about whether they felt that their decision (using antibiotics or not) was the best for them was assessed. The scale has good validity and reliability (27). The low-literacy version uses a question-and-answer format with three response options (yes, no, unsure), with scoring from 0 (low decisional conflict) to 100 (high decisional conflict) (27).

Patients' confidence in decision-making was measured using four items from the decision self-efficacy scale (28), which has high internal consistency (29). Scoring of each item is from 0 (not at all confident*)* to 100 (very confident*)*.

Data analysis

We calculated descriptive statistics (mean, standard deviation, range) for each outcome measure. Data were analysed using IBM SPSS (version 23). Benefits

and harms of antibiotics mentioned were categorised into similar groups, by description level as per ACEPP scoring, and by whether a decision aid was used.

We present the results for the whole sample in line with our original aims. However, to explore the impact of decision aids, we also present the data separately for those consultations in which a decision aid was used and not used, along with mean differences and 95% confidence intervals.

Results

Ten general practices (3 intervention, 5 control), involving 44 GPs, that had already consented to participate in the main trial or piloting of the decision aids (2 practices) by the time that recruitment for this study commenced were invited to participate in this additional study. Of these, 5 practices and 19 GPs provided consent. During the recruitment period, 208 patients were approached and 41 met the inclusion criteria. Of these, 36 patients provided consent for the recording and 25 also agreed to complete the questionnaire. The main reason given for declining to complete the questionnaire was insufficient time. We recorded 36 consultations, involving 13 GPs - 20 were for acute bronchitis, 10 for acute sore throat, and 6 for AOM. Patient, GP, and consultation characteristics are presented in Table 1.

Table 1. Characteristics of the GPs, patients, and consultations

Characteristic	**N* (%)**
GP gender – female	11 (61)
Patients	
Adults (Patient or parent)	18 (50)
Female	15 (83)
Age in years - median (min-max)	36 (18-77)
Children	18 (50)
Female	7 (39)
Age in years – median (min-max)	2 (0.8-15)
Condition	
Acute bronchitis	20
Acute sore throat	10
Acute otitis media	6
Decision aid used in the consultation	15 (42)
Consultation duration (minutes) - median (min-max)	9 (4-31)
Treatment decision (from analysis of consultation recording)	
Antibiotics	3
Delayed prescribing	7
No antibiotics	26
Treatment decision immediately post-consultation** (as reported by patients)	
Antibiotics	5
No antibiotics	20

*This is the number of consultations, GPs, or patients
** Not all patients felt sufficiently decided to report their treatment decision during the post-consultation interview.

The extent of observer-assessed SDM

The mean (SD) total OPTION score was 29.4 (12.5; range 4-54) (on a 100-point scale). The two highest scoring items were Item 12 (clinician indicates the need to review the decision) (mean=3, SD=1.5) and Item 4 (clinician lists 'options') (mean=2.2, SD=1.5). The two lowest scoring items were Item 10 (clinician elicits patient's preferred level of involvement in decision making) (mean=0.1, SD=0.3), and Item 11 (clinician indicates the need for a decision making) (mean=0.3, SD=0.5) (Fig. 3). The mean (SD) total ACEPP score was 2 (1.6) (on a 5-point scale), with Item 1 (clinician describes the treatment benefits) scoring the highest (mean=0.6, SD=0.5) (Fig. 4).

In consultations in which a decision aid was used (n=15), the mean (SD) total OPTION score was 38.8 (6.5), compared to 22.7 (11.5) for those (n=21) in which an aid was not used - a mean difference of 16 (95% CI 9.4-22.7). Similarly, the mean (SD) ACEPP score in consultations where an aid was used was 3.8 (0.5)

which was higher than those which did not 0.8 (0.8) - a mean difference of 3 (95% CI 2.6-3.5).

Discussion of antibiotic benefits and harms

Table 2 contains verbatim examples of how antibiotic benefits and harms were presented within consultations, categorised by level of description. The three most commonly discussed harms were diarrhoea, rash, and antibiotic resistance. In the 21 consultations that did not use a decision aid, the potential harms were mentioned in only 1 consultation (with nausea mentioned). Conversely, in the 15 consultations in which a decision aid was used, at least one harm was mentioned in all of them. Two harms were mentioned in 14 (93%) and 3 harms in 13 (87%) of these consultations. When benefits were discussed, those mentioned were: that antibiotics help patients' symptoms resolve faster; and reduce symptom severity, and the chance of complications. Benefits and their likelihood were explained in all 15 of the consultations where a decision aid was used. Where aids were not used, benefits were mentioned in 7 (33%) of the 21 consultations, but the likelihood of benefits described in only 1.

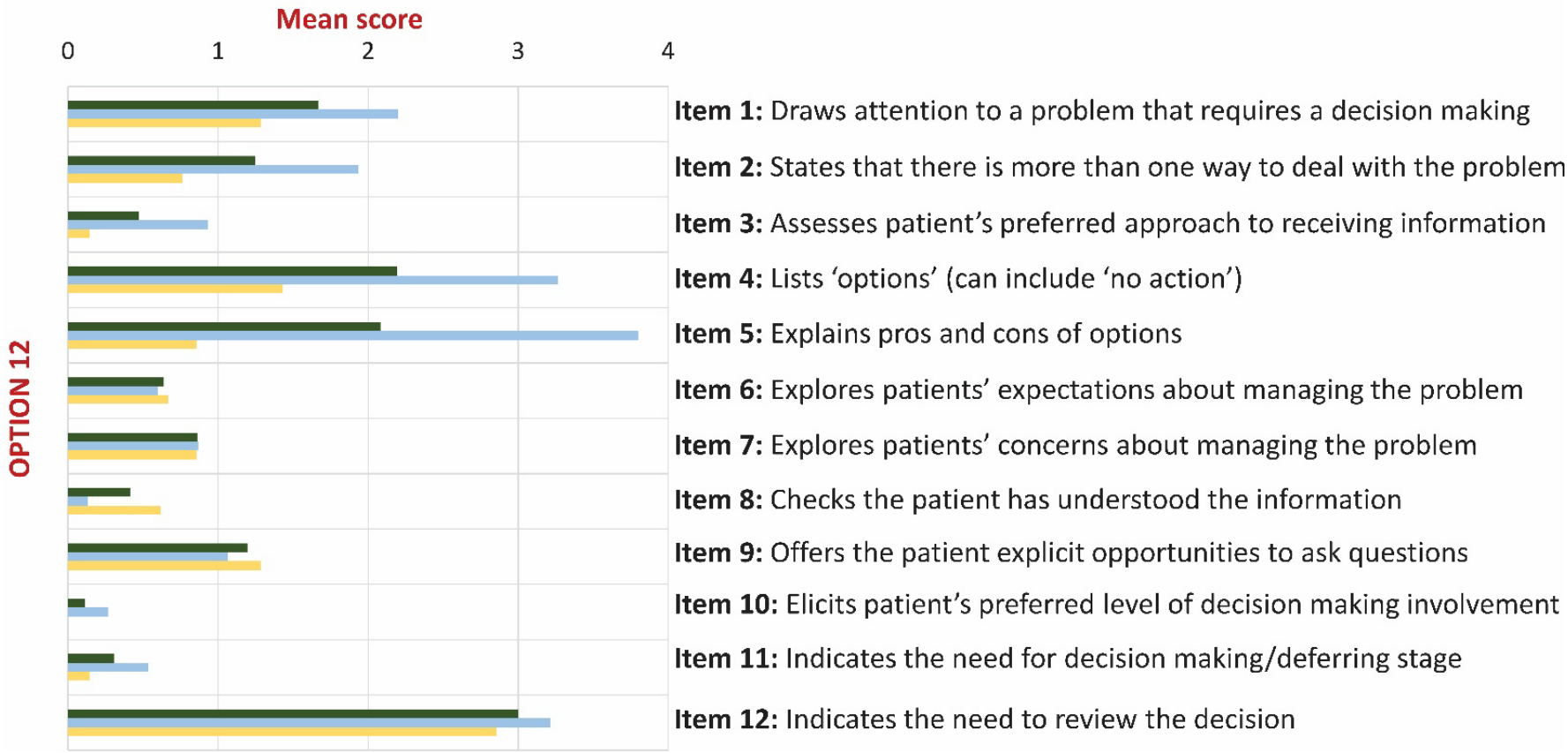

Fig. 3. Mean scores of OPTION 12 items

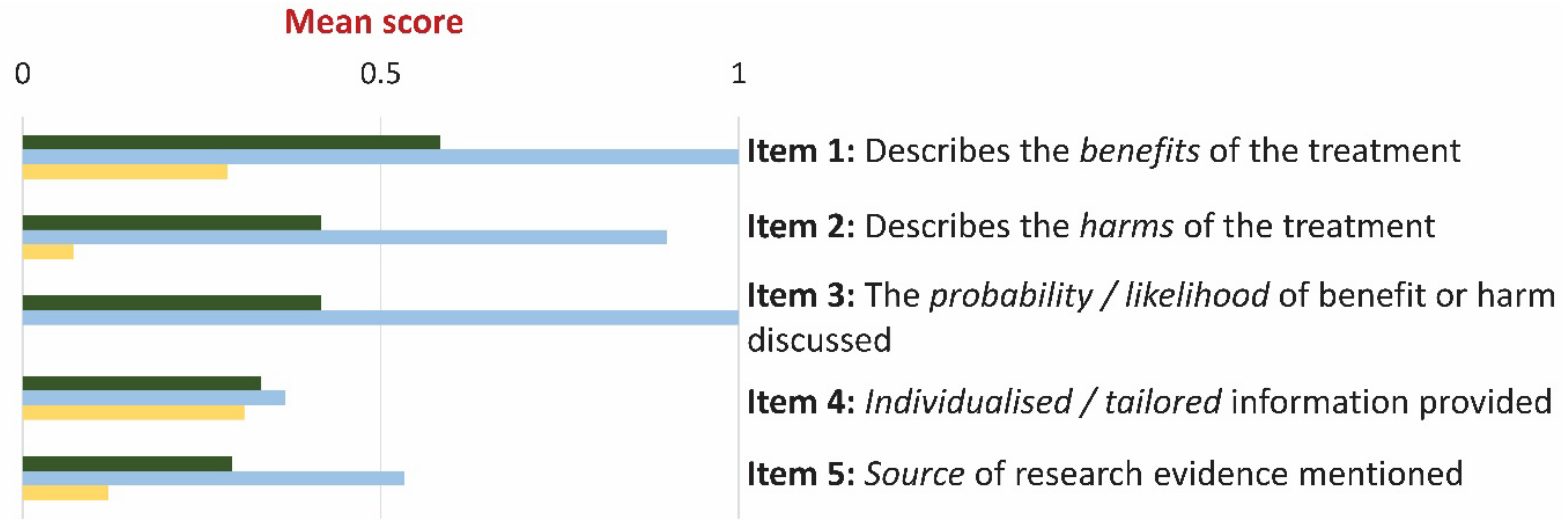

Fig. 4. Mean scores of ACEPP items about communication of benefits and harms

Table 2. Verbatim examples of how the benefits and harms of antibiotics for ARIs were presented by GPs within the consultations, grouped by level of description and whether a decision aid was used.

	Benefits of antibiotics	**Harms of antibiotics**	
		Side effects	**Resistance**
With decision aids (n= 15)	Benefits mentioned in **15 (100%) of 15** consultations	Side-effects mentioned in **15 (100%) of 15** consultations	Resistance mentioned in **10 (67%) of 15** consultations
	Mentioned to an **extended level (15/15)** *Examples:*	Mentioned to an **extended level (7/15)** *Examples:*	Mentioned to an **extended level (5/10)** *Examples:*
	GP D-2-6 "All the evidence shows if we have somebody with middle ear infection like what we have got here now…if you don't give any antibiotics the infection lasts about 3.5 days in total. If you give antibiotics it reduces that by 12 hours. It can cut off about 12 hours of the symptoms by giving antibiotics, so giving antibiotics is of limited benefit" … "so, if we look at 100 kids who don't take antibiotics, 84 will be better in 3 days. If we give antibiotics there is an extra 5 kids who would be better." **GP B-1-2** "Most sore throats get better somewhere between 2 and 7 days and that is actually whether or not you get antibiotics. Even if it is a bacterial infection you get better without antibiotics. So the treatment options are to take antibiotics or to	**GP A-2-1** "What we are looking at over here is what the potential complications maybe with antibiotics. So people who do not take antibiotics, 20 out of a 100 will have some other problems associated with the illness. Whether it be vomiting, diarrhoea or rash. Whereas if we give you antibiotics, you are more likely to have side effects or complications. So 7 more people out of a 100 …will have these potential side effects of these antibiotics. There are also other harms with antibiotics which can be having an allergic reaction, it can be the cost of buying them, remembering to take them…"	**GP A-5-2** "The other concern as well is antibiotic resistance, meaning you know the long term implications, all the good bacteria in his system being exposed to antibiotics as well they can develop some resistance, so …[if] he got meningitis in the near time and needs antibiotics, taking some will not work, because of previous resistance" **GP B-1-2** "one of the problems that a lot of the bacteria that we have had in the community for years is getting stronger and stronger and resisting the antibiotics that we have got. So we are finding this is why this shows here that only a few people finding any benefit from taking the antibiotics because there is more and more resistance in the community… but we are finding increasingly is that the more we use them for infections that your body

	not take antibiotics … This is a graph that shows you how long a sore throat would last on average. So if you take antibiotics, generally the sore throat would last about 2.6 days so just over 2 and a half days. If you do not take antibiotics on average it will last about 3.3 days, so that means it last about 16 hours longer without the antibiotics."		could probably fight them by yourself, we are actually, unfortunately, breeding bacteria that become stronger and stronger… and unfortunately at this point of time we have bacteria that is resistant to everything we have got and there is nothing new on the horizon vastly different from what we have got"
		Mentioned to a ****basic level (8/15)** *Examples:*	Mentioned to a **basic level (5/10)** *Examples:*
		GP D-2-4 "… the only problem is it increases the number of people who get rash, diarrhoea, another side effects because of the antibiotics…" **GP A-3-1** "… but then you look at the side effects and we have got all these people who do not take antibiotics obviously no side effects… and in the antibiotics you get more side effects basically. So that's each one of these little dots is someone who gets the side effect"	**GP D-2-9** "but in the big picture we are building on antibiotic resistance and you know we are coming to time where these things might not work for infections you got them to do" **GP D-2-7** "… and then you worry about antibiotic resistance and stuff like that"
Without decision aids (n=21)	Benefits mentioned in **7 (33%) of 21** consultations	Side-effects mentioned in **1 (5%) of 21** consultations	**Resistance was not mentioned in any consultations**
	Mentioned to an **extended level (5/7)** *Examples:*	No **extended level** mentions	
	GP C-1-1 "The evidence is that middle ear infection gets better 12		

	hours to 24 hours earlier if you give antibiotics and the pain is better 12 to 24 hours if you give antibiotics"	
	Mentioned to a **basic level (2/7)** *Examples:*	Mentioned to a **basic level (1/1)** *Examples:*
	GP F-1-5 "…in which case antibiotics won't do anything to get you better quicker"	**GP F-2-1** "And antibiotics would just give him side effects and upset his tummy"

****Extended level:*** The clinician explains the benefits or harms of antibiotic treatment in a manner that is clear, with elaboration on the likelihood of these occurring, *****Basic level:*** The clinician lists at least some of the benefits or harms of antibiotic treatment

Patients' perspectives of the consultation and decision-making process

The mean (SD) CollaboRATE-5 score for all consultations was 3.8 (0.4), representing high perceived patient involvement in the decision-making process. The mean (SD) Decisional Conflict score was 3.2 (8), indicating a low level of decisional conflict. Participants had high confidence in the decision made, with a mean (SD) decision self-efficacy scale score of 95 (10). There were minimal differences between the scores of patients who had, and had not, been presented with a decision aid during the consultation (Table 3).

Table 3. Mean (SD) scores of observer-assessed SDM scores and patients' perspective of the consultation and decision-making process.

Observer-assessed SDM scores (n= 36 consultations)			
	Total Mean (SD) score		
	All GPs (n= 36)	Usual Care (n= 21)	Decision Aids (n= 15)
OPTION-12 (0-100)	29.4 (12.5)	22.7 (11.5)	38.8 (6.5)
ACEPP (0-5)	2 (1.6)	0.8 (0.8)	3.8 (0.5)
Patients' perspective scores of the consultation and decision-making process (n= 25 patients)			
	Mean (SD)		
	All patients (n= 25)	Usual Care (n= 16)	Decision Aids (n= 9)
CollaboRATE-5 mean encounter score (0-5)	3.8 (0.4)	3.9 (0.3)	3.7 (0.5)
Decisional Conflict Scale (0-100)	3.2 (8)	3.1 (7)	3.3 (10)
Decisional Self-efficacy (0-100)	95 (9.9)	96.5 (6.8)	92.4 (13.9)

Discussion

Summary

Our analysis of consultations between GPs and patients with ARIs found the extent of observer-assessed SDM was generally low and the communication of antibiotic benefits and harms was also often suboptimal. In consultations in which patient decision aids were used, the discussion of antibiotic benefits and harms was more frequent and more comprehensive. When decision aids were not used, antibiotic harms were rarely mentioned, and antibiotic resistance was never mentioned.

Strength and limitations

Strengths of our study include minimising any bias from clinicians choosing which consultations to record as patient consent occurred before the consultations; two independent raters scoring the consultations; and obtaining patients' perspectives. Limitations include the design (not a true randomised trial, although it is nested within one), which might have exaggerated the effects of the decision aids; the small number of consultations and that they may be non-representative; and GPs' self-selection to participate in this additional study, which may have recruited those more confident and competent in SDM. The presence of the audio recorder in the consultation and the researcher in the waiting room may have resulted in performance bias, such as the Hawthorne effect, and inadvertently acted as a prompt for GPs to attempt or improve SDM. Also, results are limited to one country and clinicians participating may not be representative of those in other settings.

Comparison with existing literature

We know of no other studies that have objectively analysed the extent of SDM in GP-patient consultations for ARIs. Although a recent systematic review (18) of trials whose interventions had aimed to increase SDM in ARI consultations in primary care found that these interventions decreased antibiotic prescribing, none of the 10 included trials actually objectively measured whether SDM improved as a result of the intervention.

Similarly, low OPTION scores to those in this study have been reported in previous studies in different settings, such as outpatient cancer patients consulting their physicians (30), patients with back pain consulting their GPs (31), and patients consulting nutritionists about dietary treatment (32). In a systematic review of studies

that had used OPTION-12 to analyse consultations, OPTION Item 12 was one of the most consistently observed behaviours (33), and Item 10 score was very low, similar to our study.

Implications for practice and research

When decision aids were used the extent of SDM increased, including a large improvement in the frequency and quality of the conversation about antibiotic benefits and harms. Having the options with their pros and cons clearly listed in a decision aid may act as a reminder for GPs to discuss them with patients. The better discussion of antibiotic benefits and harms, including explaining the size and/or likelihood of them, is also likely due to the aids containing a very synthesized summary of the evidence about antibiotic benefits and harms. GPs may be unaware of the empirical benefits and harms data of antibiotics for ARIs. While no studies have examined GPs' knowledge of antibiotic benefits and harms, a study of paediatricians found they overestimate antibiotic benefits for ARIs (34) and generally, clinicians tend to have poor knowledge of treatment benefits and harms, overestimate benefits and underestimate harms (35).

Better benefit-harm perception by patients is necessary for informed decision making, and randomised trials have shown this improves when decision aids are used (36). In ARI consultations, improving patient benefit-harm perception is particularly important because the evidence shows near-equipoise in the benefits-harms balance, patients overestimate the benefits of antibiotics for ARIs (17, 37), and they rarely hear about the harms. Correcting these misperceptions may break the cycle of patient expectations of antibiotics as a driver of antibiotic prescribing.

Antibiotic resistance is different from the side-effects that might typically be discussed by clinicians because it is not obviously an immediate or personal consequence for the individual patient. Many members of the public have misunderstandings about what antibiotic resistance is (38) and believe that it does not affect them (39). However, it is a global problem that can affect anyone, even if indirectly, and it needs confronting. Consultations in which antibiotics are being considered for common ARIs are an ideal time to discuss antibiotic resistance as part of the benefit-harm trade-off of using antibiotics because this is an area of very high consumption. We found many missed opportunities for discussions about this to occur. Even when resistance was

mentioned, discussion was usually brief and often not clear. Clinicians' misunderstandings of antibiotic resistance have been reported in a systematic review (40).

Patients perceived that they had high involvement in the decision, despite observer-assessed SDM scores which were quite low. Reasons for this are not clear. Perhaps patients have not experienced consultations in which SDM was performed to a high level and they have low expectations of what patient involvement actually is, or perhaps the brief tool used with patients did not capture enough elements or enough similar elements that the observer-used measures did, such as whether benefits and harms were discussed. Patients also reported low decisional conflict and high confidence in their decision. This may reflect that the decision about whether to use an antibiotic for a minor illness is perceived by patients as a relatively simple one-off decision with low-stake harms. A trial of a decision aid and intense GP training to increase SDM for ARIs also reported low decisional conflict in patients in both control and intervention groups, with no statistically significant between-group difference (41).

Conclusions

This study highlights that in this convenience sample of patients with ARIs who were seeing a GP, some elements of SDM occurred during the consultation, but that there is need for improvements in the extent to which SDM occurs during such consultations, including how antibiotic benefits and harms are discussed. Patient decision aids may be part of the solution to improving this, but further research about their effect and how to support GPs to discuss antibiotic resistance with patients is needed.

Declarations

Ethics approval and consent to participate: Bond University Human Research Ethics Committee approved the study (#0000015433). A written informed consent was obtained from the participants.

Consent for publication: Not applicable

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: MB, TH and CDM conceived and designed the nested study. MB recruited patients and collected the data. MB and EG analysed the data and TH and CDM assisted with data interpretation. MB undertook the statistical analyses, created the tables and figures. MB drafted the original manuscript and EG, TH and CDM contributed to writing and revising the manuscript. All authors approved the final manuscript.

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Supplementary material

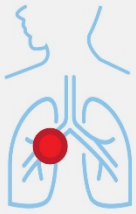
Published with article presented in Chapter 3 (Study 1)

https://doi.org/10.1186/s12875-018-0854-y

Supplementary Material 1. Acute bronchitis decision aid. A decision aid on antibiotic use for patients with acute bronchitis in primary care.
https://doi.org/10.6084/m9.figshare.7176617.v1

Acute bronchitis: should I take antibiotics?

- This decision aid is to help you decide whether to use antibiotics when **you or your child** has acute bronchitis (acute cough).
- This can help you to talk and make a **shared decision** with your doctor about what is best for you or your child.



What causes acute bronchitis?

- It can be caused by a viral or bacterial infection. It is hard for your doctor to tell which it is.
- The infection is in the airway (bronchi) leading to the lungs. Acute means it is a short-term infection.

How long does the cough last?

- The cough will usually get better by about **10-20 days**, without needing to take antibiotics.

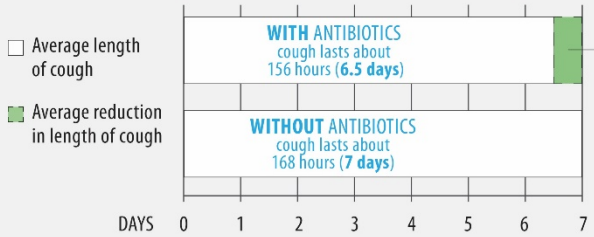
What are the treatment **options?**

There are 2 options that you can discuss with your doctor:

1. **Not taking antibiotics**
   This means letting the cough get better by itself.
2. **Taking antibiotics**

Symptoms, such as fever, can be treated with over-the-counter medicines. They can be used with either option.

What are the likely **benefits and harms** of each option?



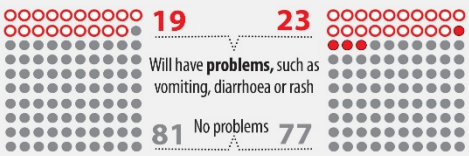
People who take antibiotics have the cough for only about **12 hours less** than people who do not.

These figures show what happens to people with acute cough who **do not** take antibiotics and those who **do**. Each circle is one person. We can't predict whether you will be one of the people who is helped or harmed.

- gets better by 1-2 weeks
- gets better by 1-2 weeks due to antibiotics
- not better by 1-2 weeks

With antibiotics, **18 more people** will be better after 1-2 weeks.

- has problems
- has problems due to antibiotics
- no problems



With antibiotics, **4 more people** will have problems like vomiting and diarrhoea. Other antibiotic harms are:

- the **cost** of buying them
- **remembering** to take them
- the risk of **antibiotic resistance** (see next page)

Where do these estimates of benefits and harms come from?

- They come from the most up-to-date medical evidence of benefits and harms about what works best. This is a review of 17 studies, and over 5000 people, that looked at antibiotic use in people with acute bronchitis.
- The quality of this research evidence is ranked as high. This means that further research is very unlikely to change these estimates.

Why might antibiotics be used?

If the infection is in the lung, it is called pneumonia. This is unlikely. However if it is pneumonia, it can be more serious. Your doctor may talk with you about why antibiotics might be needed. Coughing up coloured phlegm (spit) is not a sign that antibiotics are needed.

What is antibiotic resistance?

- Using antibiotics means the bacteria can develop resistance to the antibiotic.
- This means that **antibiotics will not work if you or your child needs them in the future** to treat a bacterial infection.
- A person who has recently used antibiotics is more likely to have resistant bacteria in their body.

Are there other things I can do?

- Fever is best treated with over-the-counter **paracetamol and/or ibuprofen**. Do not give more than the maximum recommended dose. Read the dose information on the packet.
- Aspirin should NOT be used with children who are younger than 16 years.
- Some people find that taking **honey** helps to settle the cough. Take 1-2 teaspoons, just before bedtime. The honey can be given in a drink such as warm water. Honey should not be given to children less than 12 months old.

When should you see a doctor and get further help?

If the person with the cough has any of these signs:

- Very drowsy
- Fast or difficulty breathing, wheezing, or shortness of breath
- Cold or discoloured hands and/or feet with a warm body
- Pain in the arms and/or legs
- Coughing blood
- Unusual skin colour (pale or blue) around the lips
- A rash that does not fade when the skin is pressed

Questions to consider when talking with your doctor

- ☐ Do I need antibiotics?
- ☐ What happens if I don't take antibiotics?
- ☐ Do I know enough about the benefits and harms of:
  - taking antibiotics?
  - not taking antibiotics?
- ☐ Am I clear about which benefits and harms matter most to me?
- ☐ Do I have enough information and support to decide?

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Last reviewed: November 2015. Update due: November 2017. Developed by Peter Coxeter, Professor Chris Del Mar and Professor Tammy Hoffmann - Centre for Research in Evidence-Based Practice, Bond University. Decision Aid development funded by the National Health and Medical Research Council (APP1044904).

Supplementary Material 2. Acute otitis media decision aid. A decision aid on antibiotic use for patients with acute otitis media in primary care.
https://doi.org/10.6084/m9.figshare.7176623.v1

Middle ear infection: should my child take antibiotics?

- This decision aid is to help you decide whether to use antibiotics when **your child** has a middle ear infection.
- This can help you to talk and make a **shared decision** with your doctor about what is best for your child.

What causes middle ear infection?

- It can be caused by a viral or bacterial infection. It is hard for your doctor to tell which it is.
- It is also called 'acute otitis media'. Acute means it is a short-term infection.

How long does the earache last?

- Symptoms (such as earache) usually get better in 2 to 7 days, without antibiotics.

What are the treatment **options?**

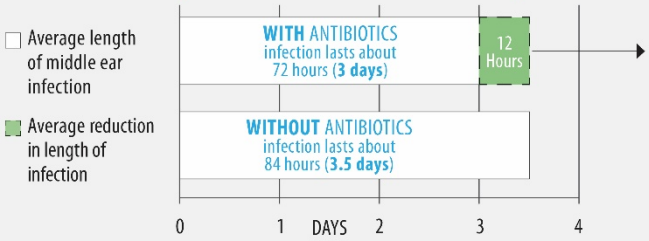
There are 2 options that you can discuss with your doctor:

1. Not taking antibiotics
This means letting the infection get better by itself.

2. Taking antibiotics

Symptoms, such as pain and fever, can be treated with over-the-counter medicines. They can be used with either option.

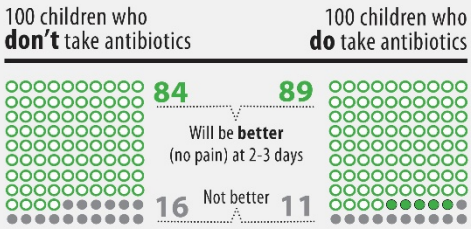
What are the likely **benefits and harms** of each option?



Children who take antibiotics have the earache for only about **12 hours less** than children who do not.

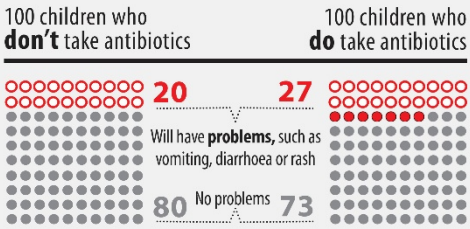
These figures show what happens to children with middle ear infection who **do not** take antibiotics and those who **do**. Each circle is one child. We can't predict whether your child will be one of the children who is helped or harmed.

- gets better by 2-3 days
- gets better by 2-3 days due to antibiotics
- not better by 2-3 days
- has problems
- has problems due to antibiotics
- no problems



With antibiotics, **5 more children** will be better after 2-3 days.

After about **4 days** most children will be better anyway - without antibiotics.



With antibiotics, **7 more children** will have problems like vomiting and diarrhoea. Other antibiotic harms are:

- the **cost** of buying them
- **remembering** to take them
- the risk of **antibiotic resistance** (see next page)

Where do these estimates of benefits and harms come from?

- They come from the most up-to-date medical evidence of benefits and harms about what works best. This is a review of 13 studies, and over 3,400 children, that looked at antibiotic use in children with middle ear infection.
- The quality of this research evidence is ranked as high. This means that further research is very unlikely to change these estimates.

Why might antibiotics be used?

There might be a special reason why your doctor may suggest antibiotics, such as in people who are more likely to get complications. This can be Indigenous children and children who are under 2 years of age.

What is antibiotic resistance?

- Using antibiotics means the bacteria can develop resistance to the antibiotic.
- This means that **antibiotics will not work if your child needs them in the future** to treat a bacterial infection.
- A person who has recently used antibiotics is more likely to have resistant bacteria in their body.

Are there other things I can do?

- Pain and fever are best treated with over-the-counter **paracetamol and/or ibuprofen**. Do not give more than the maximum recommended dose. Read the dose information on the packet.
- Aspirin should NOT be used with children who are younger than 16 years.

When should you see a doctor and get further help?

If the child with the middle ear infection has any of these signs:

- Very drowsy
- Fast or difficulty breathing, wheezing, or shortness of breath
- Cold or discoloured hands and/or feet with a warm body
- A high fever (over 38.5°C)
- Pain in the arms and/or legs
- Unusual skin colour (pale or blue) around the lips
- A rash that does not fade when the skin is pressed
- Pain and tenderness of the bone behind the ear
- Blood or discharge from the ear

Questions to consider when talking with your doctor

- ☐ Does my child need antibiotics?
- ☐ What happens if my child doesn't take antibiotics?
- ☐ Do I know enough about the benefits and harms of:
  - taking antibiotics?
  - not taking antibiotics?
- ☐ Am I clear about which benefits and harms matter most to me?
- ☐ Do I have enough information and support to decide?

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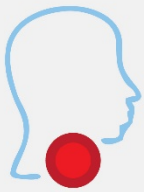
Venekamp RP, Sanders S, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev 2015;1:CD000219. www.cochranelibrary.com

Last reviewed: November 2015. Update due: November 2017. Developed by Peter Coxeter, Professor Chris Del Mar and Professor Tammy Hoffmann - Centre for Research in Evidence-Based Practice, Bond University. Decision Aid development funded by the National Health and Medical Research Council (APP1044904)

Supplementary Material 3. Sore throat decision aid. A decision aid on antibiotic use for patients with sore throat in primary care.
https://doi.org/10.6084/m9.figshare.7176632.v1

Sore throat: should I take antibiotics?

- This decision aid is to help you decide whether to use antibiotics when **you or your child** has a sore throat.
- This can help you to talk and make a **shared decision** with your doctor about what is best for you or your child.



What causes sore throat?

It can be caused by a viral or bacterial infection. It is hard for your doctor to tell which it is.

How long does sore throat last?

- Symptoms will usually get better in 2 to 7 days, without taking antibiotics.

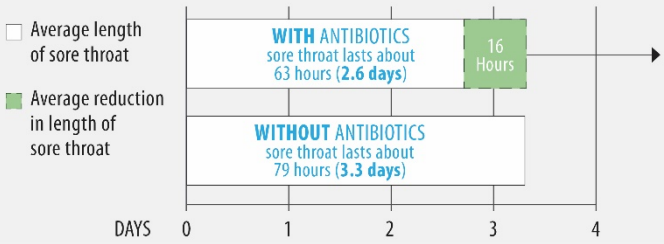
What are the treatment **options?**

There are 2 options that you can discuss with your doctor:

1. **Not taking antibiotics**
   This means letting the infection get better by itself.
2. **Taking antibiotics**

Symptoms, such as pain and fever, can be treated with over-the-counter medicines. They can be used with either option.

What are the likely **benefits and harms** of each option?



People who take antibiotics have the sore throat for only about **16 hours less** than people who do not.

These figures show what happens to people with sore throats who **do not** take antibiotics and those who **do**. Each circle is one person. We can't predict whether you will be one of the people who is helped or harmed.

- gets better by 3 days
- gets better by 3 days due to antibiotics
- not better by 3 days

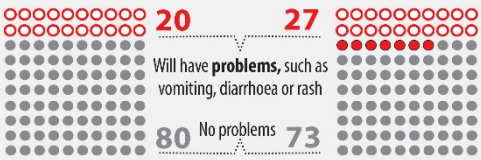
100 people who **don't** take antibiotics — 100 people who **do** take antibiotics

With antibiotics, **6 more people** will be better after 3 days.

Most people will be better after about **4-7 days** anyway - without taking antibiotics.

- has problems
- has problems due to antibiotics
- no problems

100 people who **don't** take antibiotics — 100 people who **do** take antibiotics



With antibiotics, **7 more people** will have problems like vomiting and diarrhoea. Other antibiotic harms are:

- the **cost** of buying them
- **remembering** to take them
- the risk of **antibiotic resistance** (see next page)

Where do these estimates of benefits and harms come from?

- They are from the most up-to-date medical evidence of benefits and harms about what works best. This is a review of 27 studies, and almost 13,000 people, that looked at antibiotic use in people with sore throat.
- The quality of this research evidence is ranked as high. This means that further research is very unlikely to change these estimates.

Why might antibiotics be used?

There are a few special reasons why your doctor might suggest antibiotics. This might be if the sore throat is caused by a dangerous, but rare, type of bacterium. Or in people who are at a high risk of complications, such as Indigenous people.

What is antibiotic resistance?

- Using antibiotics means the bacteria can develop resistance to the antibiotic.
- This means that **antibiotics will not work if you or your child needs them in the future** to treat a bacterial infection.
- A person who has recently used antibiotics is more likely to have resistant bacteria in their body.

Are there other things I can do?

- Pain and fever are best treated with over-the-counter **paracetamol and/or ibuprofen.** Do not give more than the maximum recommended dose. Read the dose information on the packet.
- Aspirin should NOT be used with children who are younger than 16 years.
- Gargle with warm salty water.
- Suck an ice cube or throat lozenge.

When should you see a doctor and get further help?

If the person with the sore throat has any of these signs:

- Very drowsy
- Fast, noisy, or difficulty breathing, or shortness of breath
- Cold or discoloured hands and/or feet with a warm body
- Pain in the arms and/or legs
- Unusual skin colour (pale or blue) around the lips
- A rash that does not fade when the skin is pressed

Questions to consider when talking with your doctor

- ☐ Do I need antibiotics?
- ☐ What happens if I don't take antibiotics?
- ☐ Do I know enough about the benefits and harms of:
  - taking antibiotics?
  - not taking antibiotics?
- ☐ Am I clear about which benefits and harms matter most to me?
- ☐ Do I have enough information and support to decide?

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Last reviewed: November 2015. Update due: November 2017. Developed by Peter Coxeter, Professor Chris Del Mar and Professor Tammy Hoffmann - Centre for Research in Evidence-Based Practice, Bond University. Decision Aid development funded by the National Health and Medical Research Council (APP1044904).

Chapter 4

Theme 2: Patients' understanding of aspects of antibiotic resistance and its influence on attitudes to antibiotic use

Exploring patients' understanding of antibiotic resistance and how this may influence attitudes towards antibiotic use for acute respiratory infections: a qualitative study in Australian general practice.

Mina Bakhit, Chris Del Mar, Elizabeth Gibson, Tammy Hoffmann

BMJ Open 2019;9:e026735. http://dx.doi.org/10.1136/bmjopen-2018-026735

Preamble

The previous study found that the extent of observer-assessed SDM between GPs and patients with ARIs was generally low. It also found that a more balanced and comprehensive discussion of antibiotic benefits and harms, including antibiotic resistance, occurred when decision aids were used. Study 2 aimed to explore patients' knowledge and attitudes towards antibiotic resistance and aspects of it. Examining these issues, could guide the development and/or refinement of interventions which target antibiotic use, by including appropriate and effective messages about antibiotic resistance.

This chapter presents Study 2 which was published as an article entitled *"Exploring patients' understanding of antibiotic resistance and how this may influence attitudes towards antibiotic use for acute respiratory infections: a qualitative study in Australian general practice"*.

Work arising from this chapter was presented in oral form at the Gold Coast Research Week November 14, 2018 and was also presented at the Higher Degree of Research Conference October 16, 2018 at Bond University, Gold Coast (and awarded second place for best presentations).

Abstract

Objectives— To explore patients' or parents of child patients' understanding of antibiotic resistance and aspects of resistance such as resistance reversibility and its spread among those in close proximity, along with how this may influence attitudes towards antibiotic use for acute respiratory infections (ARIs).

Design— Qualitative semi-structured interview study using convenience sampling and thematic analysis by two researchers independently.

Setting— General practices in Gold Coast, Australia.

Participants— 32 patients or parents of child patients presenting to general practice with an ARI.

Results— Five themes emerged: 1) antibiotic use is seen as the main cause of antibiotic resistance, but what it is that becomes resistant is poorly understood; 2) resistance is perceived as a future 'big problem' for the community, with little appreciation of the individual impact of, or contribution to it; 3) poor awareness that resistance can spread between family members but concern that it can; 4) low awareness that resistance can decay with time and variable impact of this knowledge on attitudes towards future antibiotic use; and 5) antibiotics are perceived as sometimes necessary, with some awareness and consideration of their harms.

Conclusions— Patients' or parents of child patients' understanding of antibiotic resistance and aspects of it was poor. Targeting misunderstandings about resistance in public health messages and clinical consultations should be considered as part of a strategy to improve knowledge about it, which may encourage more consideration about antibiotic use for illnesses such as ARIs.

Background

Antibiotics, which have been critically important for treating infections since their discovery in the 1940s, are accelerating towards weakened effectiveness due to increase in antibiotic resistance (1). Antibiotic resistance, which occurs when bacteria change in response to the use of antibiotics and resist the effects of antibiotics, is largely driven by community antibiotic use (2-4). Antibiotics are prescribed more in primary care than other health sectors, and often for acute respiratory infections (ARIs), which comprise approximately 10% of primary care consultations (5). Because of high prescribing rates, particularly for common conditions where antibiotics provide little benefit such as sore throat (6), acute otitis media (AOM) (7), and bronchitis (8), primary care is targeted for reducing antibiotic prescribing.

Understanding patients' beliefs about antibiotics and reasons for using and not using them can help inform interventions and public campaigns that aim to encourage appropriate antibiotic use (9). Research has revealed that patients overestimate the benefits of antibiotics for ARIs (10), and their expectations can influence antibiotic prescribing (11).

Research that has explored the public's understanding of antibiotic resistance, consequences of it, and whether patients consider the threat of resistance when deciding, ideally in conjunction with their clinician, whether to use antibiotics is scarce (9,12). There are also aspects of antibiotic resistance that might affect perceptions about antibiotic use, but patients' understanding of and views about these have not been investigated. This includes that antibiotic use increases resistance in the period following use, but this resistance decays with time (4), and that resistance can be transmitted between people in close proximity such as family and household members (13). How knowledge of this might influence patients' beliefs about antibiotic use for minor self-limiting illnesses such as ARIs is unknown. Such information is needed to ensure that clinical consultations and public health campaigns about antibiotic use cover all the appropriate and relevant key messages.

This study aimed to explore, in a sample of patients, or parents of child patients, presenting to a general practitioner (GP) directly after the decision-making point

in a clinical encounter for ARI, their understanding of: 1) antibiotic resistance in general; and 2) aspects of antibiotic resistance, including resistance decay and spread among people in close proximity, and how attitudes towards antibiotic use may be influenced by this understanding.

Methods

Design

This was a qualitative study which used semi-structured interviews to explore participants' understanding of antibiotic resistance and implications for decisions about antibiotic use.

Participants and setting

Recruitment and the interviews occurred in general practices in southeast Queensland, Australia that had been recruited as part of an ongoing cluster randomised trial (14). The trial intervention that was provided to the general practices was three patient decision aids (for acute otitis media [AOM], acute sore throat, and acute bronchitis) and a 15-minute video that demonstrated shared decision making. Practices randomised to the control group did not receive any active intervention.

Recruitment of participants for this study occurred between September 2016 and June 2017 from both the intervention and control practices. Practice managers' approvals were obtained through email communication and recruitment days were organised according to each practice's preference. Patients were eligible to participate if they met these criteria. The first was that they were an adult (or parent of a sick child) 18 years or older consulting a consenting GP with one of three ARIs (AOM, acute sore throat, acute bronchitis) for the first time for that illness episode. We recruited adults and children as both experience ARIs and with a few exceptions, the benefits and harms of antibiotics for ARIs, along with the risk and consequences of antibiotic resistance, are similar for both groups. Other criteria were that participants could understand and read English and provide written informed consent.

Patient and public involvement

No patients or members of the public were involved in the design of this study. However, they were involved in the development of the decision aids used by GPs in some of the

recruited general practices. Patients were involved in this study as participants. The results of this study were disseminated to interested study participants by email.

Procedure

The interviews were conducted by one author (MB), using an interview topic guide (summarised in Box). The topic guide was developed based on a systematic review of relevant literature (12), and findings from a cross-sectional study of Australian parents' experiences of ARI management and antibiotic use in primary care (10). The questions were piloted with two eligible participants who were not recruited into the study, and minor rephrasing of some questions occurred after piloting.

Some practices organised a room for the interviews, whereas at other practices, the interviews occurred in a private area of the waiting room. The recruitment process differed according to each practice's preference. At some practices, the interviewer (assisted by practice staff) approached only patients who were waiting to see the GPs who were participating. At other practices, the interviewer approached all waiting patients and asked if they were waiting to see one of the participating GPs (GP names were listed and shown to patients). If so, recruitment proceeded. Patient eligibility was determined by asking the patients if they were suffering from one of the following symptoms (sore throat, cough, ear pain), with the diagnosis confirmed afterwards by the treating GP. Potential participants were provided with a verbal explanation of the study and a written study information sheet. After confirming eligibility and obtaining written consent, each participant was interviewed for an average of approximately 15 minutes directly after leaving the consultation room. Patients were interviewed directly after the consultation because this is: i) for most, the time of decision making about whether to take antibiotics, ii) important for reducing recall bias, and iii) enabled face-to-face interviews to occur. Interviews were audio-recorded, with participants' consent, and transcribed verbatim afterwards. The interview recording was deleted if a patient was diagnosed by their GP as having an illness other than an ARI. This occurred for one recording as the patient had a cough from a chronic illness.

Box. Summary of topic guide for interviews

- 'Usual' approaches of expecting and/or using antibiotics for managing ARIs, including beliefs about necessity of antibiotics, their benefits and harms, and other influences on decision-making about antibiotic use
- Understanding of the meaning of 'antibiotic resistance', its cause/s, and implications of it. *[If the participant did not know what resistance was, the interviewer provided a brief explanation before proceeding to next questions]*
- Awareness that antibiotic resistance can spread between those in close proximity (such as family and household members) and if unaware, reactions to being told that it can
- Awareness that antibiotic resistance can decay over time and if unaware, reactions to being told that it can

Data analysis

After 26 participants had been interviewed, a preliminary thematic analysis was undertaken. It was decided that data saturation had not occurred, and recruitment of participants continued until data saturation was obtained at 32 participants. This was defined as when no new ideas or constructs emerged from two consecutive interviews.15 Two authors (MB and EG) then independently used the process for thematic analysis outlined by Braun and Clark.16 After familiarising themselves with the interview transcripts, they generated overarching themes and subthemes. This was a data-driven process that was partially inductive in nature. The authors compared and discussed their themes and analyses and with the input of an additional researcher (TH), came to consensus. The themes and illustrative quotes were then agreed to by all authors.

Results

Participant characteristics

We approached 208 patients in five general practices: 41 met the inclusion criterion of having an ARI, and of these, 32 (18 adult patients and 14 parents of sick children) consented to participate. The most common reason given for declining participation was insufficient time to be interviewed. Participants' mean age was 38 years (range 18-74), the majority were female (n= 25, 78%), and half (n= 16, 50%) were consulting for an episode of acute bronchitis (Table 4).

Table 4. Participant characteristics

Participant ID	Participant age (years)	Gender	Presenting condition	If child, age (years)
P01	18	Female	Sore throat	
P02	73	Male	Acute Bronchitis	
P03	34	Female	Acute otitis media (AOM)	1
P04	47	Female	Sore throat	
P05	37	Female	Sore throat	1.3
P06	34	Female	Unspecified ARI	11
P07	38	Female	Acute Bronchitis	
P08	28	Female	Acute Bronchitis	
P09	32	Female	Acute Bronchitis	2
P10	22	Male	Acute Bronchitis	
P11	27	Female	Sore throat	
P12	64	Male	Acute Bronchitis	
P13	52	Male	Acute Bronchitis	3
P14	39	Male	Acute Bronchitis	2
P15	36	Female	AOM	6
P16	43	Female	Acute Bronchitis	3
P17	18	Female	Sore throat	
P18	43	Female	Sore throat	
P19	70	Female	Acute Bronchitis	
P20	45	Female	Sore throat	
P21	34	Male	Acute Bronchitis	
P22	30	Female	AOM	4
P23	74	Female	Acute Bronchitis	
P24	25	Female	Acute Bronchitis	1.3
P25	24	Female	Sore throat	
P26	18	Female	Acute Bronchitis	
P27	36	Female	Unspecified ARI	3
P28	21	Male	Unspecified ARI	
P29	50	Female	Unspecified ARI	
P30	34	Female	Acute Bronchitis	2
P31	38	Female	Acute Bronchitis	4.5
P32	35	Female	AOM	1.8

Themes

Five themes emerged, and these are presented below and supported by illustrative quotes.

Theme 1. Antibiotic use is seen as the main cause of antibiotic resistance, but *what* it is that becomes resistant is poorly understood.

Many participants thought that antibiotic overuse or misuse in people drives antibiotic resistance - *"Sometimes people think they need antibiotics. That's where they can lead to resistance because they have them too much"* (P03); with a few mentioning other reasons such as antibiotic use in animals; *"Through our food, that sort of thing, it does seem to be a concern now. Like, animals getting fed antibiotics"* (P12); or not using the full antibiotic course *"But if you use them … you don't take the full dose, obviously like in that you've got your certain bugs coming out."* (P25).

Nearly all participants thought that antibiotic resistance is when the body becomes resistant to antibiotics:

> *"Antibiotic resistance, your body is resistant to it and maybe you've used too much of it… antibiotics"* (P16)
>
> *"Antibiotic resistance is possibly your body, rejecting the benefits of the antibiotics … it's almost like the body gets used to the antibiotic"* (P10)
>
> *"If you take antibiotics too regularly, your body stops, reacting to them, or they stop having an impact"* (P04)

Some participants still had misperceptions after the interviewer provided a simple explanation of what antibiotic resistance is (*"Antibiotic resistance happens when bacteria change to protect themselves from an antibiotic. They are then no longer killed by that antibiotic")*:

> *"Oh, yeah, see I've never had that sort of problem. I've never heard it. Whenever I've taken it, maybe I wasn't sick enough to sort of resist it. It's always worked. And for the time that I had to take more than once, a repeat, you know."* (P23)

Theme 2. Resistance is perceived as a future 'big problem' for the community, with little appreciation of the individual impact of, or contribution to it

Most participants perceived antibiotic resistance as a community problem caused by others who misuse antibiotics:

> *"… if people are over using it. Yeah, especially with their children when they're so young. If they're regularly on antibiotics, yeah…."* (P06)

> *"I imagine there would be some pockets of the community that it* [antibiotic resistance] *might be an issue for."* (P04)

> *"I think it's a big problem. People like to get antibiotics and just solve things instantly. Like people don't like to wait and see what happens, they like to get something – even if they think it's going to work or not, they just – something to make it better."* (P15)

Most participants described resistance as a problem that will not impact them individually - "*I don't think it's a big issue for me"* (P09); *"I think I'll get through my life without it impacting on it"* (P21). A few participants described their worry about antibiotic resistance, although by many it was viewed as a future or a hypothetical concern:

> *"Oh, huge, I don't want that to happen… Um, well, if she got sick and constantly needed antibiotics… you know, then obviously in - as she gets older, they'd stop working as much as you wouldn't be able to treat infections as much and I don't want that to happen"* (P03)

> *"… it could become a big problem if the so-called superbugs, um, come out and about later on, yeah."* (P09)

> *"It still concerns me, um, because someone as young as my two-year-old son – I guess in an older person, it's perhaps not as concerning because over the course of a life time... but I think the message is out there that maybe you need to think twice before* (using antibiotics*)"* (P09)

Theme 3. Poor awareness that resistance can spread between family members but concern that it can

Most participants did not know that antibiotic resistance can spread between people who are in close proximity, such as family members - *"No, I didn't even know it could spread"* (P24). Some thought it would be possible:

> *"Um, I've never really thought about it before. My initial answer would be no, but I guess like if – yeah I guess if one of the children had a bug that was tougher, and they gave that to the other child, then, yeah, I guess, yeah, I guess it would be"* (P32).

When participants were told by the interviewer that it can, the most common reaction was concern *"concerned. Yeah, it's not a good thing"* (P14) and shock *"Oh, shocked. No, I never knew that."* (P01), with some insight into the significance of the problem *"So by one person using antibiotics can create problems for the whole family… Yeah. Well, that's, um, not real good, is it?"* (P19)

Some participants suggested strategies to minimise the spread of resistance such as decreasing antibiotic use *"…. so not using them too much"* (P03) or with hand hygiene (*"hand sanitiser"* (P21), *"wash hands"* (P07)).

Theme 4. Low awareness that resistance can decay with time and variable impact of this knowledge on attitudes towards future antibiotic use

Most participants did not know that antibiotic resistance could decay over time:

> *"Oh, I've got no idea, I thought it just – that it stayed for a lifetime if you were resistant to it."* (P24)

> *"Oh, a long time. You'd have to - it'd take a lot of different ways to treat it"* (P03)

> *"I imagine not, because once it's in your system, it remains there"* (P09)

There was wide variation on estimation of the time to decay, ranging from days to decades:

> *"It wouldn't be; you wouldn't think within a couple of days… but I'm not saying 12 months or anything like that"* (P19)

"Oh, probably ten years or something, crazy" (P15)

After explanation from the interviewer that antibiotic resistance does decay, some participants were more hopeful about the problem of antibiotic resistance:

"…it's promising to know that there is a chance … given enough time, then they [Antibiotics] could work again" (P21)

"Yeah, well that's good that it could be then reversible" (P32)

"It makes me think that you could possibly go back to using those antibiotics if you had the similar problem maybe 18 months down the track" (P10)

It was assumed by some that science will come up with solutions to manage antibiotic resistance in the future:

"I don't think it will go away, but I think maybe people are coming up with different solutions to fight it rather than antibiotics or different ways of switching off you know our body's responses and things like that." (P15)

"It will be interesting over the next 10-15 years. I think that probably there'll be some really good break throughs in -- in the engineering and the science behind antibiotics…" (P21)

The impact of knowing about resistance decay on attitude towards antibiotic use was variable. Some participants indicated no change (*"No different than I said before. If it means it's* [antibiotics] *going to save my life and help me in my health, it wouldn't make any difference at all.* (P23)), whereas others expressed that knowing this made them more cautious:

"That makes me really think about it – taking antibiotics only if you really need to" (P08)

"Especially for the children it would a lot scarier that they wouldn't be able to be treated … if they were sick and something. It's quite frightening." (P22)

Theme 5. Antibiotics are perceived as sometimes necessary, with some awareness and consideration of their harms

Antibiotics were seen as beneficial by many participants (*"only thing that helps"* (P20)). The most commonly reported perceived benefits were decreased duration

of illness (*"taking antibiotics would make me better quicker"* (P11)) and decreased severity or progression of the infection (*"to make sure it doesn't go to any further stages of infection."* (P06)).

Some participants believed in the need for antibiotics, despite being told by their GP that antibiotics would not help with viruses or provide better outcomes for them:

> *"… the doctor said oh it's a virus, I said well I'm going to be looking after my grandchildren, it's school holidays, and I needed something to help me get over this. …and she said but they are not going to help you. I said well it's my decision at the time to have them because I didn't want my children to have what I had, you know. It was just a very bad virus I had, you know. But anyway, the antibiotics did work."* (P23)

Some participants were reluctant to take antibiotics for minor self-limiting illnesses, such as ARIs, and preferred to reserve antibiotic use for severe infections - *"I would be hesitant. So, yes, maybe each time my doctor gives me antibiotics, I would ask is that necessary?"* (P07), with some concerned about not wanting to overuse antibiotics - *"should be more carefully applied and perhaps conservatively used."* (P18). Others' attitudes about antibiotic use were not influenced by illness severity - *"…doesn't really change my opinion of it… certain antibiotics really work"* (P25). Some participants' reasons for not using antibiotics were to *"give the body the best fighting chance"* (P15) and by *"trying natural healing and staying healthy in the first place"* (P13)

The few participants who had personal experience of antibiotic resistance were particularly cautious about antibiotic use:

> *"…because of my bronchitis… I have taken other medications that haven't worked. The – the doctors then had to change it… to a different medication. Yeah. Because I become resistant to others so I'm very fussy about taking them."* (P20)

There was great variability in participants' awareness of the potential harms of antibiotics. Many participants named potential side-effects with commonly listed ones including "*vomiting*", "*nausea*", "*thrush*", and "*diarrhoea*". Some mentioned

"*possible resistance*" as one of their concerns, but responses conveyed misunderstanding of what antibiotic resistance actually is. Some participants were not aware that antibiotics had potential harms - "*None that I'm aware of"* (P21).

The patient-clinician relationship was viewed as very important when decisions about the management of infections were being made. Trust in the clinicians' recommendation for antibiotic use was mentioned by some - "*as long as I can talk to my doctor and trust that the doctor is making the right decision"* (P05)

Some participants described a lack of information and discussion with their clinician *"I don't have enough information to probably correctly make that call."* (P18) and were unaware of the option to not treat with antibiotics (that is, that the illness would get better without them) *"Um, well I guess when it's infected there's not really much other choice for that particular problem"* (P32).

Some expressed a desire for more information about antibiotic resistance:

> *"Um, yeah, it would be good to know more about, um, how often you have to be taking them for resistance to build, whether individual, patient to patient"* (P18).

> *"… interested in knowing more information about* (antibiotic resistance)*"* (P15)

Discussion

This study has identified five major themes that related to people's understanding of antibiotic resistance and aspects of resistance such as resistance reversibility and spread among those in close proximity such as family or household members. While many participants articulated the link between antibiotic use and resistance, there was confusion about the nature of antibiotic resistance, which was often attributed to a trait of the body rather than bacteria in the microbiome. Many saw antibiotic resistance as a potential problem, rather than one that exists already, and that it was a consequence of and problem for the others in the community rather than them as an individual. Few appreciated the potential for antibiotic resistant organisms to spread between those in close proximity, or that antibiotic resistance can decay.

Most participants reported the main benefit of antibiotic use was a decreased duration of illness. Some were aware of the potential for harm from antibiotics, including resistance. Some expressed reluctance to use antibiotics for minor self-limiting infections because of concern about overuse or misuse, whereas for others, it was not because of the potential harms but because of a preference for allowing their body to fight the infection naturally.

The poor understanding of the nature of antibiotic resistance has been found in previous studies in a general practice setting (17) and in non-healthcare settings (18-20). A recent survey of the UK general adult population showed that lack of antibiotic resistance awareness was strongly associated with self-reported likelihood of requesting antibiotics for an influenza-like infection (21). It appeared that patients who had personal experience of antibiotic resistance were the most reluctant to use them again, preferring to reserve their use for serious illness. A survey of the general population in Germany found that people who knew of someone suffering from multidrug-resistant organisms, received more information by their clinician on antibiotic resistance and took less antibiotics for an infection (of any cause), compared with people who did not have any personal involvement (19).

Our finding that the lack of individual 'ownership' of contribution to, or risk of, antibiotic resistance has previously been identified in a systematic review (12), which showed that the public do not believe they contribute to the development of antibiotic resistance. This is complemented by the finding that some participants believe that science will find a way to solve the resistance problem, which contradicts with messages about individuals needing to change their behaviour to minimise the problem.

Many public health campaigns convey the message of antibiotic resistance and how it is promoted by inappropriate antibiotic use and misuse. The effect of some campaigns has been analysed and a decrease in antibiotic use was found (22, 23). Some of our findings might be useful in guiding and refining the content of messages in public health campaigns and clinical consultations about antibiotic resistance. For example, the information that developing antibiotic resistance in one's microbiome might also lead to resistance in people who are physically close to them, such as family members, could be an additional message in patient and

public educational strategies to encourage appropriate antibiotic use. Most participants were quite concerned upon learning about resistance spread and it prompted some to provide suggestions for how to minimise resistance development and its spread – suggesting that perhaps this is the information that could contribute to altering people's attitudes and behaviour about antibiotic use for minor self-limiting illnesses.

Future research into the optimal information about antibiotic use and resistance to include in public messages and clinical consultations is recommended. This includes the potential utility of information about resistance decay and its impact on antibiotic use. Knowing that resistance decays over time if antibiotics are not used promoted hope in some people that the problem of resistance was not irreversible and that efforts to conserve antibiotic effectiveness by not using unless essential are worthwhile. However, for others, knowing that resistance decay occurs over time, may thwart attempts to encourage responsible antibiotic use.

At a clinical consultation level, better engagement with patients when antibiotics are being considered by providing a balanced discussion of antibiotic benefits and harms is encouraged. This conversation should include discussion that resistance is a potential harm of antibiotic use, and explanation of the possible consequences of it for the individual and the broader community.

A limitation of our study is that the sample is not representative of the wider Australian population as participants were recruited from one city in Australia, only those presenting with an ARI were invited, and the majority of participants were female. For a small number of participants (9), there is the risk that their knowledge about antibiotic resistance was influenced by their GPs' use of a patient decision aid - which included a very brief explanation of what resistance is, but not about the spread or decay of resistance. Although GPs who did not receive or use the aids may have mentioned resistance as part of the consultation regardless. Other limitations are that participants did not have the opportunity to provide feedback on the themes derived from the interviews and the short duration of the interviews—which could have affected the depth of the gathered information. Strengths of the study include the use of two researchers independently performing the thematic analysis and its contribution of new

findings to this field. We are not aware of other studies which have explored people's knowledge about the potential for antibiotic resistant organisms to spread between those who are in close proximity or that antibiotic resistance decays over time.

Conclusion

This study found that patients' understanding of many aspects of antibiotic resistance was poor including: what it is, individual contribution to its development, individual implications, its spread and decay. Incorporating messages that target misunderstandings into public health messages and clinical consultations may be an important strategy to encourage more appropriate use of antibiotics for illnesses such as ARIs.

Declarations

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Ethics approval: Ethical approval was provided by the Human Research Ethics Committee at Bond University (#0000015433) and consent provided by each participant interviewed and by GP practices to allow recruitment of their patients.

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Chapter 5

Theme 3a: Evidence about resistance development and decay

Resistance decay in individuals after antibiotic exposure in primary care: a systematic review and meta-analysis.

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Preamble

The previous studies in (Chapters 3 and 4) discussed the importance of GPs and patients having a balanced discussion about antibiotic benefits and harms during consultations about ARIs. Including antibiotic resistance as one of the harms of using antibiotics in this discussion is a valuable way to improve patients' understanding of antibiotic resistance and implications of antibiotic use. As part of the antibiotic use decision, clinicians may wish to consider the timeframe to resistance decay after antibiotic use.

A previously published systematic review showed that antibiotic use is associated with increased isolation of resistance organisms up to 12-month after antibiotic exposure in primary care (1). However, as explained in Chapter 2, there is a need to update the evidence behind antibiotic resistance decay and to explore if the decay behaviour varies by antibiotic class or type of bacterium.

This chapter consists of the paper titled "*Resistance decay in individuals after antibiotic exposure in primary care: a systematic review and meta-analysis"*, published in BMC Medicine. It examines the development and decay of bacterial resistance after antibiotic use in individuals from the community.

Work arising from this chapter was also presented in oral form at the National Medicines Symposium 2018 in Canberra. Additionally, this work was presented as a poster at the Higher Degree of Research Conference 2016 at Bond University, Gold Coast, where it won "Best Poster Award-by judges".

Abstract

Background— Antibiotic resistance is an urgent global problem, but reversibility is poorly understood. We examined the development and decay of bacterial resistance in community patients after antibiotic use.

Methods— This was a systematic review and meta-analysis. PubMed, EMBASE and CENTRAL (from inception to May 2017) were searched, with forward and backward citation searches of the identified studies. We contacted authors whose data were unclear, and of abstract-only reports, for further information. We considered controlled or times-series studies of patients in the community who were given antibiotics and where the subsequent prevalence of resistant bacteria was measured. Two authors extracted risk of bias and data. The meta-analysis used a fixed-effects model.

Results— Of 24,492 articles screened, five controlled and 20 time-series studies (total 16,353 children and 1461 adults) were eligible.

Resistance in *Streptococcus pneumoniae* initially increased fourfold after penicillin-class antibiotic exposure (odds ratio (OR) 4.2, 95% confidence interval (CI) 3.5–5.4), but this fell after one month (OR 1.7, 95% CI 1.3–2.1). After cephalosporin-class antibiotics, resistance increased (OR 2.2, 95%CI 1.7–2.9); and fell to (OR 1.6, 95% CI 1.2–2.3) at one month. After macrolide-class antibiotics, resistance increased (OR 3.8, 95% CI 1.9–7.6) and persisted for one month (OR 5.2, 95% CI 2.6–10.3) and three months (OR 8.1, 95% CI 4.6–14.2, from controlled studies and OR 2.3, 95% CI 0.6–9.4, from time-series studies).

Resistance in *Haemophilus influenzae* after penicillins was not significantly increased (OR 1.3, 95% CI 0.9–1.9) initially but was at one month (OR 3.4, 95% CI 1.5–7.6), falling after three months (OR 1.0, 95% CI 0.5–2.2). Data were sparse for cephalosporins and macrolides.

Resistance in *Enterobacter* increased post-exposure (OR 3.2, 95% CI 0.9–10.8, from controlled studies and OR 7.1, 95% CI 4.2–12, from time-series studies), but was lower after one month (OR 1.8, 95% CI 0.9–3.6).

Conclusions— Resistance generally increased soon after antibiotic use. For some antibiotic classes and bacteria, it partially diminished after one and three months, but longer-term data are lacking and urgently needed.

Review registration—PROSPERO CRD42015025499.

Background

The discovery of penicillin in the mid-20th century heralded the antibiotic era (2, 3), and contributed significantly to a decrease in the rates of morbidity and mortality that had been caused by previously life-threatening infections (4, 5) However, antibiotic resistance emerged shortly afterwards (6). This drove the discovery of new antibiotics (5). However, the development of new antibiotics is no longer keeping up with resistance (7) and we now face the threat of a post-antibiotic era (8-10).

Antibiotic resistance is generated by its use (8). One area of interest is the high use of antibiotics in primary care, particularly for the treatment of acute respiratory infections, for which there is very little or no benefit (11-15) Yet many clinicians in primary care persist, believing that resistance is not their problem (16-18).

Systematic reviews suggest that prescribing antibiotics in primary care initially increases the prevalence of resistant bacteria in patients—more so in countries with higher prescribing rates (19) – but that they became less detectable in the microbiome after 12 months (1). The return of the microbiome to antibiotic susceptibility is critical in encouraging a reduction of antibiotic use, which is being actively pursued in the primary-care community internationally to minimise antibiotic resistance. What remains unknown is the time this takes, and how it varies by antibiotic class and bacterium.

This information is important for informing public health messages, antibiotic resistance campaigns and clinician training. This systematic review aimed to identify and synthesise prospective studies that have examined the occurrence of bacterial resistance in community-based patients who were exposed to antibiotics, and to explore whether resistance decay varies by antibiotic class and bacterium.

Methods

We initially planned simply to update a previous systematic review that had addressed resistance decay (1). However, we were unable to replicate the search (since there were discrepancies in the numbers of studies found and differences in the eligible and included studies identified) and also realised that the time

points were poorly discriminated, especially those from retrospective studies. The design of retrospective studies means that: 1) they can report only the time interval between antibiotic exposure and the isolation of resistant isolates at the end of the study, with no data in between; 2) details of the exposure antibiotic, such as type and dose, are often unknown and 3) there is often a selection bias towards patients with treatment failure. Accordingly, we undertook this review de novo.

This research was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) (20).

Eligible study designs

Eligible studies compared antibiotic-exposed participants to controls (including randomised controlled trials or RCTs), or involved prospective repeat measure cohorts that reported the prevalence of resistant bacteria among patients, isolates or specimens (percentage of resistant isolates from each swab) over time. Retrospective studies were also identified as part of the same search process but will be reported separately. Case reports were ineligible.

Eligible participants

We included studies of patients (or isolates from them), of any sex or age, symptomatic or asymptomatic, who were treated in the community or had community-acquired infections. Studies that included patients with hospital-associated infections, device-related infections and persistent infections were ineligible (Supplementary Material 4).

Eligible types of antibiotic exposure

We included any study in which participants in the index group were exposed to a short antibiotic course (≤2 weeks), of any antibiotic class.

Eligible comparison

Groups of participants who either did not use antibiotics (controls) or used them at different times were eligible as comparators.

Outcomes

The primary outcome was the isolation of resistant bacteria at a pre-specified time point. Studies that did not report the duration between the last known antibiotic exposure and isolation of resistant bacteria, or did not report the before and after prevalence of resistant and susceptible isolates in studies comparing two antibiotic exposures, were excluded.

Search and information sources

We searched PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception until the first week of May 2017, using medical subject headings (MeSH) and keywords: 'Drug Resistance' AND 'Anti-Bacterial Agents' AND 'Primary Health Care' AND 'Patients' with a detailed search strategy (Supplementary Material 5). Forward and backward citation searches identified additional relevant studies. We contacted authors whose data were unclear, and of abstract-only reports, for further information.

Study selection

Two researchers (MB and JR) independently screened the titles and abstracts of search results using Endnote (version X8) and the Rayyan website for systematic reviews (21), and then the full texts of remaining studies for inclusion. A third reviewer (CDM or TH) resolved any disagreements.

Data extraction

Two researchers (MB and AS) used a pre-specified and pre-piloted form to independently extract data on: study design, study duration, symptomatic or asymptomatic patients, age, recruitment location, total number of reported patients and isolates, methods of sampling, and collection of antibiotic exposure data and analysis. Disagreements were resolved by consensus or third author (CDM or TH).

Assessment of risk of bias

Two researchers (MB and AS) independently evaluated the risk of bias, using the Cochrane Risk of Bias tool (22) for RCTs, or, for other study designs, items

adapted from the Risk of Bias in Non-Randomised Studies, Interventions (ROBINS-I) tool (23) (Box 2).

Box 2. Items adopted from ROBINS-I tool for the included cohort studies

- **Bias due to confounding:**
  - Confounding factors were adjusted in the analysis (low risk)
  - Confounding factors were measured and showed balance (low risk)
  - Randomised comparison (low risk)
- **Bias due to missing data (Follow-up data):**
  - Bias that arises when later follow-up is missing for individuals initially included (low risk <20 %)
- **Bias in measurement of outcomes (who measured resistance):**
  - Independent lab (low risk)
  - Independent technician (low risk)
  - Study researchers (high risk)

Data analysis

We derived the odds of identifying resistance at different time points. Some studies limited the denominator to participants carrying bacteria and others to total participants (those carrying bacteria or not). We included only data from participants carrying bacteria, which enabled comparisons, as we are interested in the burden of resistance on the community. We extracted incident cohort counts, where reported. If they were not, we manually calculated them from odds ratios (ORs). When resistance data were reported for more than one antibiotic, we analysed only resistance to the same antibiotic to which participants were exposed (to avoid duplication), and co-resistance data were extracted and reported in separate tables. Some studies reported resistance as 'intermediate' and 'high': we collapsed these into 'resistant'.

We use the term 'prospective repeated measures cohort studies' to describe those that were randomised trials by design but in which the data were extracted from each arm of the trial separately without the benefit of randomisation. These were analysed with the cohort studies. The main study designs are detailed in Table 5.

Resistance prevalence data can be compared at different time points in two ways, according to study design: a separate control group (methodologically more

robust) or studies reporting before and after antibiotic exposure. We meta-analysed the two methods separately, but present them adjacently.

To facilitate comparisons, we collapsed the reported time periods after antibiotic exposure to pre-specified ranges: pre-exposure and from end of treatment (i.e. time 0): 0 to ≤1 week, >1 week to ≤1 month and >1 to ≤3 months. When the same study reported multiple resistance data that fell in the same pre-specified ranges, we chose the latest time point provided. We undertook the meta-analysis using RevMan Version 5.3 (24), pooling Peto ORs from the end of treatment with a fixed-effects model to correct better for zero cell counts (22). We assessed statistical heterogeneity among studies with a $\chi 2$ test (using $P \leq 0.05$ for significant heterogeneity) and I^2. Subgroup analyses were pre-specified by the time since last antibiotic exposure. We were not able to test for statistical differences between different times using either a statistical test for trend or a $\chi 2$ test for heterogeneity of the different time subgroups, as some studies provided data for different time points, but not all.

Protocol and registration

The review protocol was registered on the PROSPERO database (CRD42015025499) at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42015025499 . Ethics approval was not required. A modification of the protocol was to clarify that studies that had reported resistant bacteria at the isolate level were also eligible (Appendix 4 Systematic review protocol).

Results

Study selection

Our search found 24,117 citations, supplemented by 5878 citations identified from forward and backward searches of references cited in included studies, which, after removing duplicates, left 24,492. Screening by title and abstract excluded 23,934, leaving 558 for which the full text was screened. After excluding 379 (Supplementary Material 6 gives detailed reasons for exclusion), 179 eligible articles remained, of which 25 studies (in 26 articles) assessed the isolation of resistant bacteria prospectively. These were included in this review (Fig. 5).

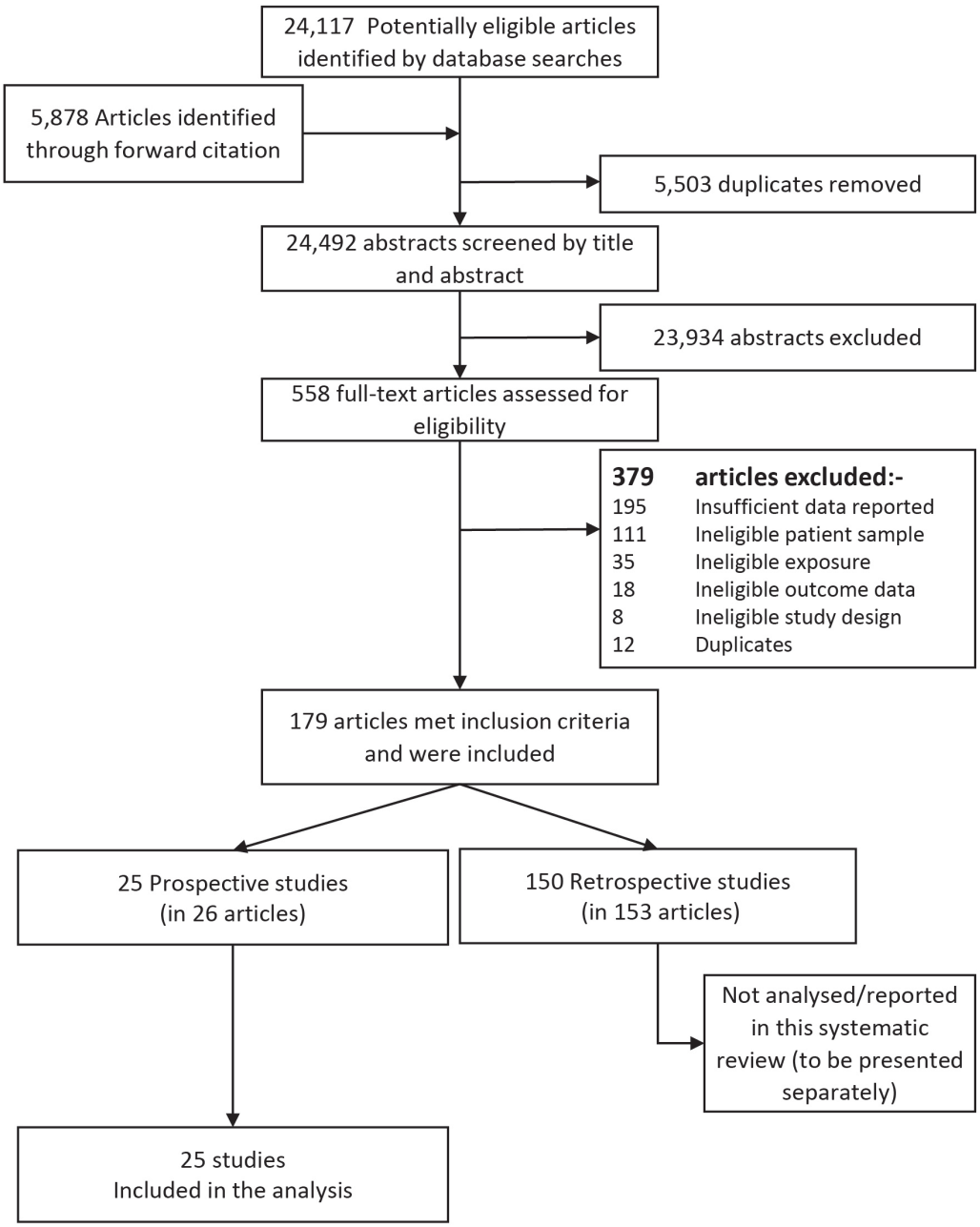

Fig. 5. Study flow chart

Study characteristics

Of the included studies, five were RCTs (25-29) and 20 were prospective cohort studies (30-50). We report the study design here in relation to the outcome of resistance, although some studies were RCTs for the outcome of efficacy. Table 5 shows study characteristics. All but three (26, 29, 39) were conducted in one of the Organisation for Economic Co-operation and Development countries (OECD countries):

- 16 investigated children (total of 16,353) (26, 29-34, 36-41, 44, 45, 48-50), and 8 studied adults (total of 1,461) (25, 27, 28, 35, 42, 43, 46, 47)
- 14 investigated symptomatic patients, (12 with respiratory infections (28, 30-34, 36-38, 48-50); 1 with urinary infections (42); 1 with acute febrile illness (47))
- 6 involved asymptomatic participants (25, 27, 29, 35, 43, 46)
- 5 studies included both (26, 39, 41, 44, 45).

Twelve compared antibiotic exposure against a control or placebo (25-31, 39, 41, 43, 45, 47), and 13 were antibiotic comparison studies (32-38, 42, 44, 46, 48-50). Antibiotics from the following classes were studied: penicillins (14) (28, 30-38, 41, 48-50); macrolides (12) (25-27, 29, 37, 39, 41, 44, 46, 49, 50); cephalosporin (8) (31-33, 36-38, 49, 50); sulphonamides and trimethoprim (2) (42, 45); quinolones (1) (46); lincomycin (1) (43), ketolides (1) (35) and one study included any antibiotic (47).

Risk of bias in studies and heterogeneity assessment

The risk of bias was assessed based on the study design for the outcome of resistance, not the original study design for the outcome of efficacy. The overall risk of bias was low, although bias due to selective reporting was uncertain for most RCTs because resistance was often not nominated as an outcome and there was an unclear risk of bias for the outcome measurement in the cohort studies (Fig. 6). We were not able to test for publication bias for the examined outcomes because of the very low number of studies in each funnel plot (Supplementary Material 7). There was considerable variation in the heterogeneity between studies, particularly for the cohort studies (Figs. 7, 8 and 9).

Table 5. Characteristics of included

	Setting	*Study Design			Participants		**Total number of participants	Age range		Sample site		Method of measuring resistance						Guidelines used			Sampling time points					
					S	AS																			
		RCT	COS - Nested in a RT	COS with a control group	Adults	Children		From	to	Respiratory	Gastrointestinal Tract	Agar-dilution	Disk-diffusion	E Test	Paper disk testing	Broth-dilution method	ASS	NCCLS/CLSI	CASFM/EUCAST	German National S.	Not reported	Baseline	End of treatment	Days	Weeks	Months
Murray et al.[45] (Mexico 82)	?		✓		?		145	?			✓	✓	✓								✓	✓		14		
Huovinen et al.[42] (Finland 85)	hCC		✓		✓		97	16 y	64 y		✓	✓									✓	✓	✓			1
Brook, I[30] (USA 88)	PED			✓		✓	54	?		✓		?								✓		✓		7 to 10	5 to 7	3
Eliasson et al.[38] (Sweden 90)	hCC		✓			✓	150	0 m	10 y	✓					✓						✓	✓	✓		4	
Cohen et al.[32] (France 97)	PED		✓			✓	364	4 m	4.5 y	✓		✓			✓			✓				✓		2 to 6		
Dagan et al.[37] (Israel 98)	ER			✓		✓	120	3 m	3 y	✓			✓					✓				✓		4 & 5		
Dabernat et al.[36] (France 98)	PED & ENT		✓			✓	426	6 m	3 y	✓			✓					✓	✓			✓	✓			1
Cohen et al.[33] (France 99)	PED		✓			✓	513	4 m	2.5 y	✓		✓			✓			✓				✓		12 to 14		1
Chern at al.[26] (Nepal 99)	V	✓				✓	122	1 y	10 y	✓				✓							✓	✓		14		
Ghaffar et al.[40] (USA 99)	PED		✓			✓	160	6 m	6 y	✓				✓	✓			✓				✓			2	2
Morita et al.[44] (USA 00)	S			✓		✓	300	?		✓				✓				✓				✓		17, 32		
Varon et al.[50] (France 00)	PED			✓			705	3 m	3 y	✓		✓									✓	✓	✓	2 to 6		
Schrag et al.[48] (Dominican R. 01)	hOC		✓				795	6 m	5 y	✓				✓				✓				✓		5, 10, 28		
Ghaffar et al.[41] (USA 02)	PED			✓		✓	160	6 m	6 y	✓				✓	✓			✓				✓			2	2
Cremieux et al.[35] (France 03)	hCC		✓			✓	50	19 y	44 y	✓			✓								✓	✓	✓	14, 21,45		
Berg et al.[25] (Netherlands 04)	hOC	✓				✓	296	54 y	73 y	✓				✓				✓				✓	✓			2
Toltzis et al.[49] (USA 05)	PED		✓		✓		1009	3 m	7 y	✓				✓				✓				✓		3 to 5, 10 to 12		1
Gaynor et al.[39] (Nepal 05)	V		✓		✓	✓	444	12 m	7 y	✓						✓		✓								6
Lofmark et al.[43] (Sweden 06)	Vol		✓			✓	8	31 y	58 y		✓	✓					✓	✓				✓	✓		3	3, 6, 9, 12, 18, 24
Conradi et al.[34] (Spain 07)	hER			✓	✓		134	0 m	5 y	✓		✓						✓				✓	✓			1
Malhotra-Kumar et al.[27] (Belgium 07)	Vol	✓				✓	224	18 y	58 y	✓							✓	✓				✓		8, 28		
Chung et al.[31] (UK 07)	GP		✓		✓		119	6 m	12 y	✓				✓			✓	✓				✓			2, 12	
Raum et al.[47] (Germany 08)	GP			✓	✓		541	mean=57.5			✓						✓			✓		✓		7, 14		
Nord et al.[46] (USA 09)	OC		✓			✓	143	18 y	45 y	✓				✓				✓				✓	✓		2, 4, 6	
Skalet et al.[29] (Ethiopia 10)	V	✓				✓	10778	12 m	10 y	✓				✓							✓					3
Malhotra-Kumar et al.[28] (Europe 16)	PC	✓			✓		102	20 y	81 y	✓							✓	✓				✓	✓	8, 14, 28, 42		6

*Study design reported is based on the type of extracted data; ** Numbers might be different from those included in the analysis

S= Symptomatic, AS= Asymptomatic; PED= Paediatric clinics, hOC= Hospital outpatient clinic, GP= General practices, S= School, OC= outpatient clinic, hCC= health care centre, hER= hospital emergency department, V= villages, Vol= volunteers, PC= Primary care; ASS= Automated Antimicrobial Susceptibility Testing Systems; RCT= Randomised-controlled trials, COS= Prospective cohort study design, RT= randomised trial; NCCLS/CLSI = The Clinical and Laboratory Standards Institute , CASFM/EUCAST= French/EUropean Committee on Antimicrobial Susceptibility Testing

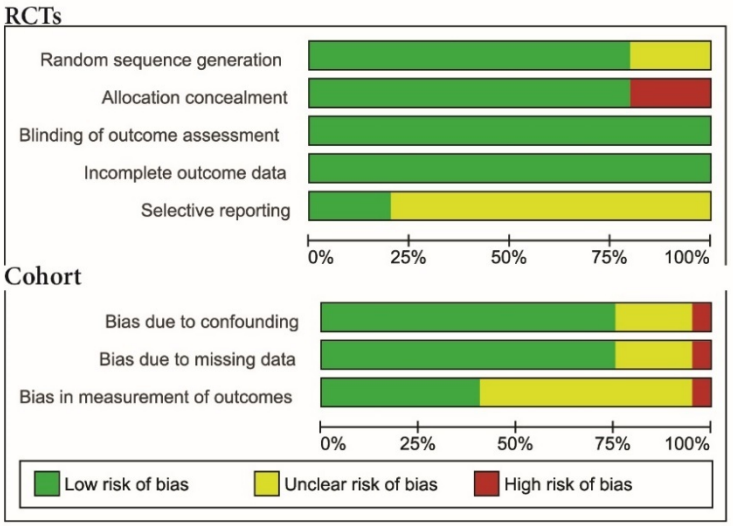

Fig. 6A. Risk of bias graph for RCTs and Cohort studies

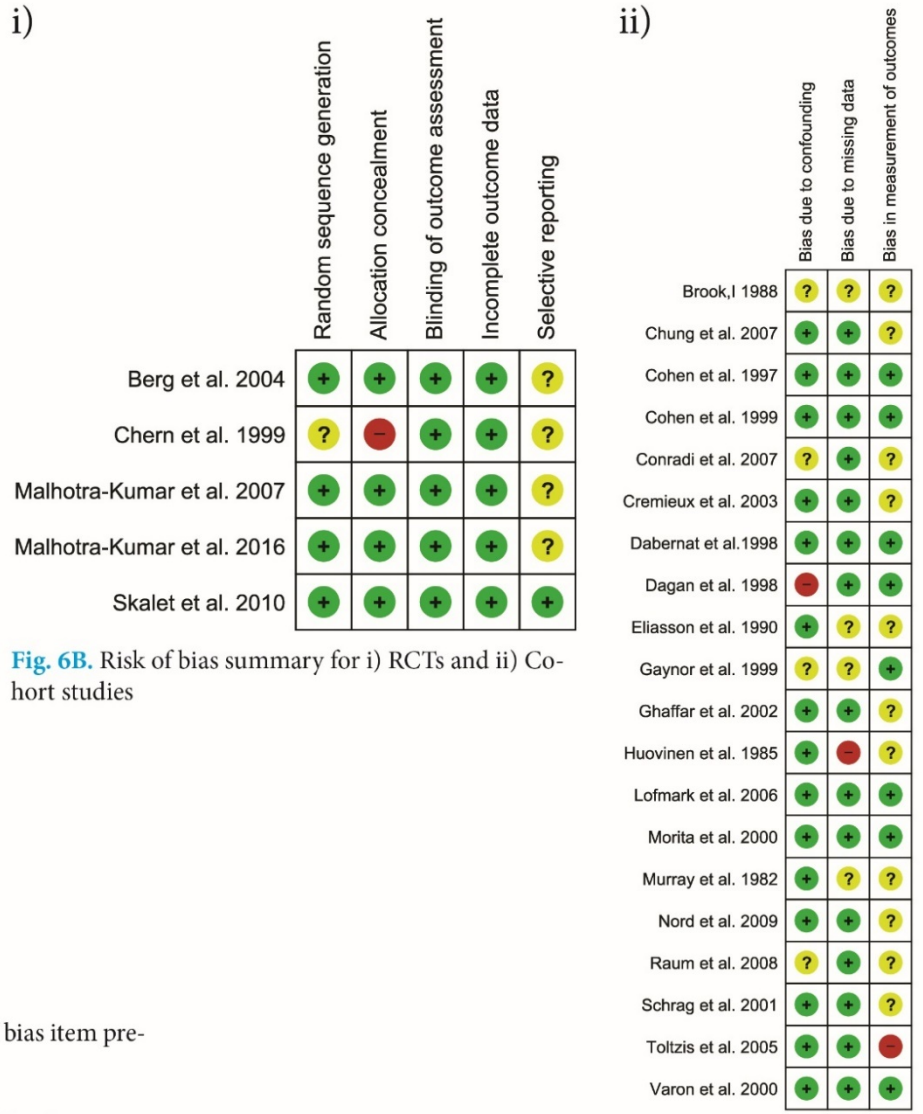

Fig. 6B. Risk of bias summary for i) RCTs and ii) Cohort studies

Fig. 6A. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies

Fig. 6B. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Resistance in respiratory tract bacteria

Bacteria were isolated from the respiratory tract in 19 studies and from the conjunctiva in one study.

Streptococcus pneumoniae and penicillin exposure

Penicillin-resistant *Streptococcus pneumoniae* were studied in only one controlled study (with 35 participants). Before exposure to penicillin, resistance was not significantly different between the group of patients subsequently exposed and those not exposed [OR 2.8, 95% confidence interval (CI) 0.5–15.3]. After exposure, the OR of resistance in those exposed was 9.4 (95% CI 0.6–149.3). After 3 months, there was no longer a significant difference in resistance (OR 0.4, CI 0.02–9.8; Fig. 7).

There were more data from prospective repeated measures cohort studies that compared resistance rates before antibiotic exposure (baseline data) and after penicillin exposure after 1 week (0 to 7 days; 6 studies, 1060 participants and 8 antibiotic exposure groups) and after 1 month (>1 week to ≤1 month; 4 studies, 772 participants and 5 antibiotic exposure groups). After 1 week, resistance had increased significantly (OR 4.2, 95% CI 3.3–5.4). Thereafter, resistance had reduced after 1 month (OR 1.7, 95% CI 1.3–2.1; Fig. 7).

One RCT (28) investigated reported resistance in isolates (rather than individuals) after exposure to amoxicillin and its data are analysed separately. It found that the changes in resistance following amoxicillin exposure were short-lived, returning to normal by 1 month after the end of treatment (Fig. 7).

S. pneumoniae and cephalosporin exposure

There were no RCTs. Four cohort studies (519 participants and 8 different antibiotic exposure groups) reported that resistance had increased at 1 week after exposure (OR 2.2, 95% CI 1.7–2.9), persisting after 1 month (OR 1.6, 95% CI 1.2–2.3; Fig. 7).

S. pneumoniae and macrolide exposure

There were three controlled studies. After a month, one small study reported the OR of resistance was 6.3 (95% CI 0.4–103.2). In three studies (437 participants),

it remained high (OR 8.1, 95% CI 4.6–14.2) at 3 months. An RCT (27) of isolates found that a single course of macrolide-class antibiotics caused increased resistance in the first week immediately after macrolide use, and resistance remained significantly higher than the placebo group for more than 3 months (data not shown).

Three cohort studies (101 participants and 3 different antibiotics) reported increased resistance at 1 week (OR 3.8, 95% CI 1.9–7.6). Three studies (147 participants and 3 different antibiotics) found that after 1 month, resistance was increased (OR 5.2, 95% CI 2.6–10.3). There were 3-month data from only one study (OR 2.3, 95% CI 0.6–9.4; Fig. 7).

Haemophilus influenzae and penicillin exposure

Two RCTs (117 participants) found comparable resistance between groups before exposure to penicillin (OR 0.8, 95% CI 0.4–1.7). One week after exposure, resistance had increased non-significantly in one RCT (with only 4 participants; OR 7.4, 95% CI 0.2–374). Increased resistance persisted for 1 month in another RCT (102 participants; OR 3.4, 95% CI 1.5–7.6). At 3 months, in this study, resistance had returned to normal (OR 1.0, 95% CI 0.5–2.2).

In four cohort studies (356 participants and 5 different antibiotic exposure groups), resistance was not increased at 1 week (OR 1.3, 95% CI 0.9–1.9). In two of the four cohort studies (183 participants and 3 different antibiotic exposure groups), it remained not increased at 1 month (OR 1.3, 95% CI 0.7–2.2; Fig. 8).

H. influenzae and cephalosporin exposure

There were no RCTs. Three cohort studies (229 participants and 3 different antibiotic exposure groups) found resistance had not increased at 1 week (OR 1.2, 95% CI 0.7–1.9) or at 1 month (255 participants; OR 1.3, 95% CI 0.9–2; Fig. 8).

H. influenzae and macrolide exposure

One RCT (175 participants) reported data at two time points. Before exposure, resistance was not significantly different between groups (0.6, 95% CI 0.3–1.3) and directly after macrolide exposure, resistance had increased in the exposed group (OR 2.5, 95% CI 0.8–8.2). One cohort study also reported two time points.

Resistance had increased after exposure at 1 month (OR 2.0, 95% CI 0.3–12.9) and it had decreased by 3 months (OR 0.5, 95% CI 0.1–3.1; Fig. 8).

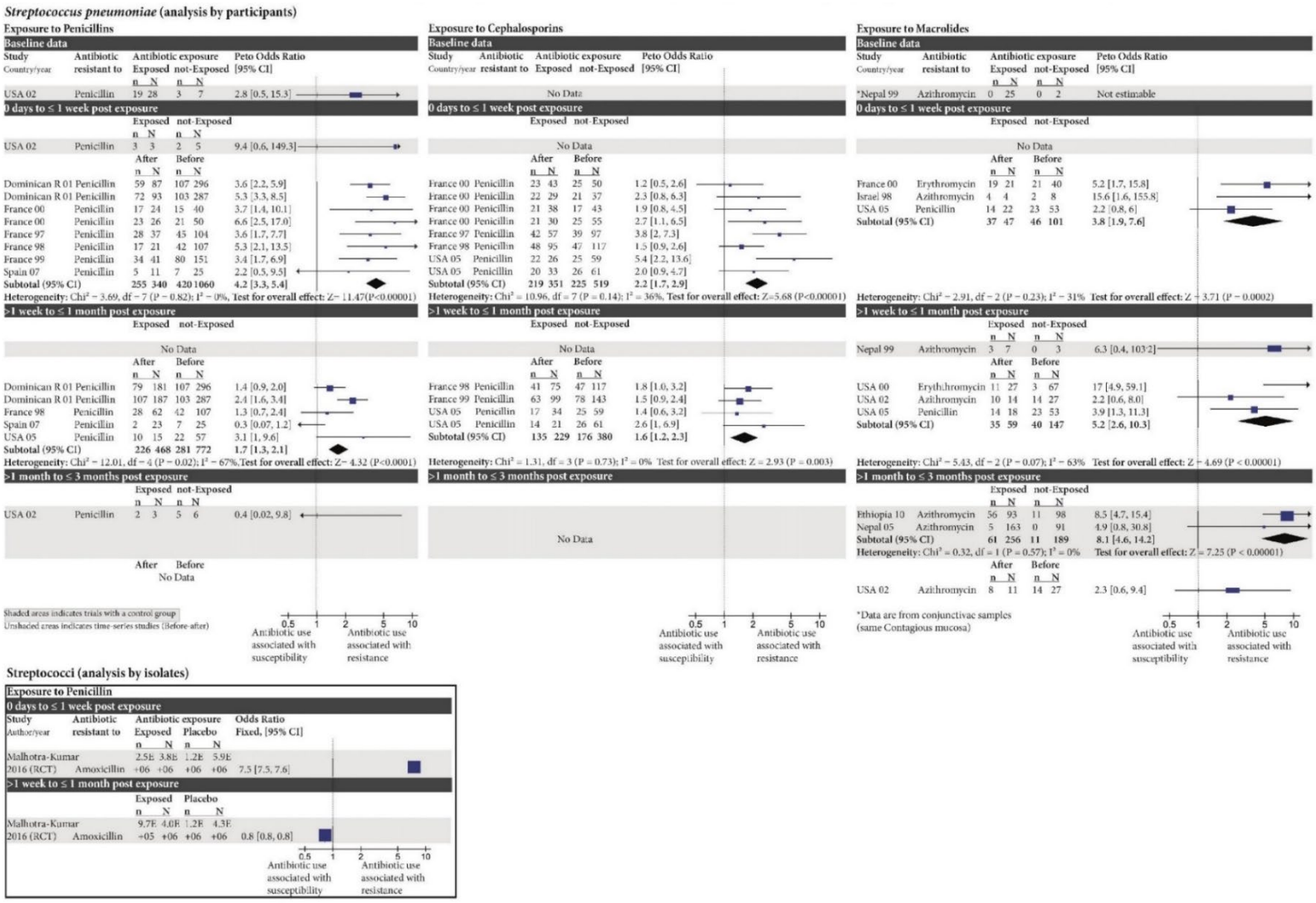

Fig. 7. Pooled ORs for resistance in respiratory tract bacteria (*Streptococcus pneumoniae*) and antibiotic exposure by class. Studies grouped by time from the end of antibiotic exposure

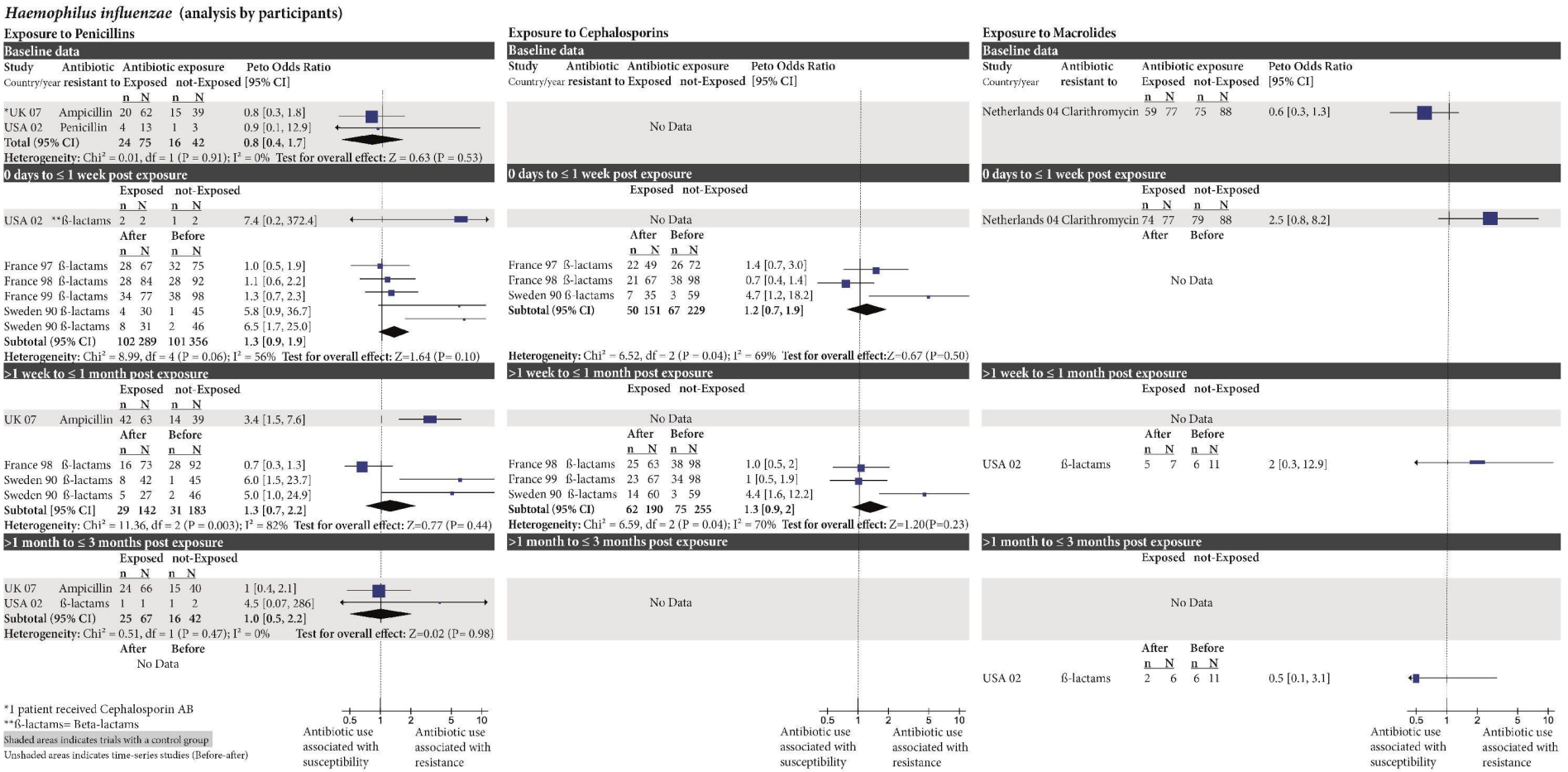

Fig. 8. Pooled ORs for resistance in respiratory tract bacteria (*Haemophilus influenzae*) and antibiotic exposure by class. Studies grouped by time from the end of antibiotic exposure

Resistance in other respiratory bacteria

The heterogeneity in five studies of resistance to *non-groupable streptococci*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *beta-lactamase producers* and *Streptococcus mitis*, exposed to different antibiotic classes (penicillins, cephalosporins, macrolides, ketolides and quinolones), precluded meta-analysis. However, Supplementary Material 8 shows a forest plot for the studies.

Resistance in Gram-negative gastrointestinal tract bacteria to several antibiotics

Trimethoprim and β-lactams exposure: In one RCT (with 64 participants), before antibiotic exposure, the OR of isolating resistance was not significantly different at 0.8 (95% CI 0.3–2.3). Two controlled studies (with 179 participants) compared antibiotic exposure against a group with no exposure. It found that 1 week after antibiotic exposure, the OR of isolating resistant Gram-negative bacteria was 3.2 (95% CI 0.9–10.8; Fig. 9).

Trimethoprim and trimethoprim-sulfamethoxazole exposure: From two cohort studies (129 participants and 3 different antibiotic exposure groups) the OR of isolating antibiotic-resistant *Enterobacteria* was 7.1 (95% CI 4.2–12) at 1 week. In one study (with 93 participants and 2 different antibiotic exposures), the OR was 1.8 (95% CI 0.9–3.6) at 1 month (Fig. 9).

One RCT (43) investigated the consequences of a 1-week course of clindamycin on Bacteroides species using isolates rather than participants as the unit of analysis. It reported that the numbers of isolates returned to pre-treatment levels after 3 weeks in the exposed group. However, the isolates demonstrated qualitative changes to their diversity, and resistance genes remained 2 years later (data not shown).

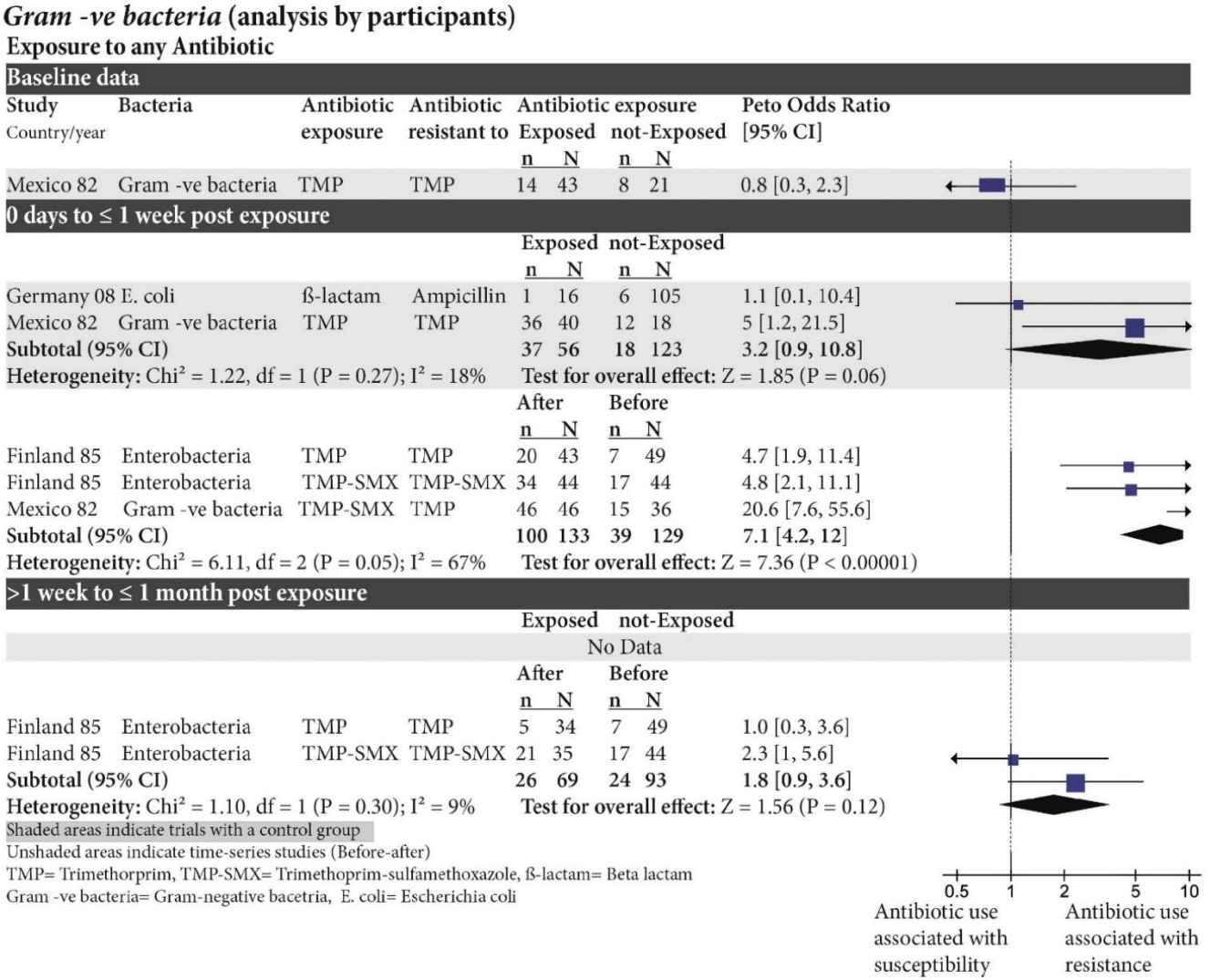

Fig. 9. Pooled ORs for resistance in Gastrointestinal tract bacteria and antibiotic exposure by class. Studies grouped by time from the end of antibiotic exposure

Co-resistance in participants in included studies

Nine of the included studies reported selection for resistance to a different antibiotic than the exposure antibiotic (co-resistance). In respiratory isolates, 3 months after azithromycin exposure, the OR of isolating clindamycin-resistant *S. pneumoniae* (OR 4, 95% CI 1.6–10.1) and erythromycin-resistant *S. pneumoniae* (OR 2.1, 95% CI 1.1–3.9) was significantly higher between exposed and unexposed groups. In gastrointestinal tract *Enterobacteria*, there was a significant increase in the odds of isolating trimethoprim-resistant bacteria immediately after exposure to trimethoprim/sulfamethoxazole (OR 4.5, 95% CI 1.8–11.7; Supplementary Material 9).

Discussion

Our systematic review found that antibiotic resistance in either the respiratory or gastrointestinal tracts of people in the community increased immediately after treatment with any of the antibiotics studied. This generally decayed over the next month, particularly in *S. pneumoniae* isolates treated with penicillins. The effect of cephalosporins on resistance was less pronounced at 1 week but persisted for at least for a month. After macrolide exposure, resistance persisted for at least 3 months. The paucity of controlled studies means there is some uncertainty around the estimates of the rate of decay of resistance in the macrolides.

There was no significant difference in isolation of resistant *H. influenzae* following penicillin or cephalosporin exposure. For macrolides, there were not enough data to examine this. For Gram-negative bacteria in the gastrointestinal tract, resistant bacteria were detectible 1 month after antibiotic exposure, decaying from immediately after exposure.

Antibiotic resistance may well predate the human exploitation of antibiotics (51). Our data show that baseline antibiotic resistance increases after antibiotic use. The mechanism by which this happens includes selection of bacteria with the pre-existing gene and the acquisition of the resistance gene from other organisms in the microbiome. Similar mechanisms may be operating in the reversal of resistance when antibiotics disappear from the host environment.

This review, with its more up-to-date collection of studies, more rigorously collected data (from only prospective studies) and more precise time frames (which avoid the uncertainty implicit in time-until periods dictated by retrospective designs), confirms the broad finding of previous systematic reviews that antibiotic exposure results in resistance (1, 19).

It has been reported previously, that isolation of resistant isolates was strongest in the month directly after exposure and remained detectable for up to 12 months (1). However, our review provides better and more nuanced estimates of the time to decay of antibiotic resistance after exposure, with faster decays than previously reported. In addition, we show that the time frame may vary according to antibiotic class and bacteria, notwithstanding the limitations of the primary evidence.

Our search strategy was systematic and transparent, and found studies that had not been found in the earlier review of resistance decay (1). Our review also provides a higher level of rigour by excluding studies at high risk of bias due to confounding variables (such as hospitalisation, device-associated infections and persistent infections) and by being careful to align the time periods after antibiotic exposure (as subgroup analyses) among the included studies to enable better comparisons.

There are several limitations of this review. First, the unadjusted status of the ORs we extracted, rather than simply importing study authors' adjustments of some confounders, threatens to introduce bias from those confounders. There are potentially many other confounders. For example, resistance can be acquired through contact with other individuals rather than direct antibiotic exposure, groups within the included studies may have different baseline risks for resistance, resistance sampling was not standardised and indications for antibiotic exposure and bacterial load (likely to differ between symptomatic and asymptomatic participants, who might be the only carriers of resistance in their microbiome, or between children and adults) might affect the development of resistance. However, the crude ORs reported differ little from the adjusted values.

We were not able to investigate any effect of dose or duration of the antibiotic exposure on resistance. The quality of how resistance data were analysed and reported was poor in some studies, and some authors did not respond to our

requests to clarify aspects of their methods and data, which contributes to the uncertainty of the review's estimates. This could be because reporting of resistance was not the primary objective in most of the included studies. Finally, resistance was reported in most studies as the proportion of resistant isolates, which does not take account of the changes in overall bacterial population, which is likely to decrease from the antibiotic effect. Consequently, a rise in the resistance proportion might disguise a decrease in the absolute numbers of resistant bacteria.

Urgently needed is further research with high-quality placebo-controlled trials that measure the numbers of resistant and susceptible isolates and enable comparisons of antibiotic dose, duration and class against different bacteria.

Conclusions

Antibiotic use increases the consequent isolation of bacterial resistance in individuals. The odds of resistance developing and the time of return to bacterial susceptibility may vary by antibiotic class. It appears that decay after exposure to antibiotics may be faster than previously reported (1) for penicillins against respiratory *S. pneumoniae*, and perhaps *H. influenzae*, although this may not be true for other antibiotics such as macrolides, where resistance might persist longer. This may be another factor for clinicians to consider when choosing an antibiotic, especially for minor infections. More primary research focussing on resistance development and decay is needed to further inform clinical decisions and public health policies.

Declarations

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Availability of data and materials: The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions: MB, CDM and TH designed the study. MB and JR undertook the screening. MB and AS carried out the data extraction and quality assessment. MB, CDM, EB and TH undertook the statistical analysis. MB created the tables and figures and prepared the supplementary material. MB, CDM and TH drafted the original manuscript. All authors revised and approved the final manuscript.

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Competing interests: The authors declare that they have no competing interests.

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Supplementary material

Published with article presented in Chapter 5 (Study 3)

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Supplementary Material 4. Elaboration on the inclusion and exclusion criteria

	Inclusion criteria	**Exclusion criteria**	**Rationale for exclusion criteria**
Population	Symptomatic and asymptomatic patients (healthy people)	Hospitalised patients with infections >48 hours after admission	Increased risk of colonization with drug-resistant bacteria from the hospital environment
	Hospitalised patients with a community infection (<48 hours from admission)	Patients with post-surgery infections	
		Burn-associated infections	
		Sample of health care workers, medical or nursing students with medical rotations	
		ICU patients referred from hospital wards or patients with central-line associated bloodstream infections	High probability that these patients are infected with resistant bacteria
		Patients with device-related infections (catheter, implants, dialysis-associated infections, ventilation-associated infections)	Devices are more prone to infection with resistant bacteria
		Patients with persistent diseases (Tuberculosis, H. pylori, Syphilis, Pseudomonas aeruginosa, Mycobacterium leprae, Salmonella typhi)	Asymptomatic infections that remains undetected for a long duration. They require prolonged antibiotic treatments and it is considered treatment failure if the bacterium is isolated after treatment.
		>50% of the sample are	Infections due to

		Immunocompromised patients	opportunistic bacteria that normally does not cause infections
		Patients with (Cystic fibrosis patients, Bronchiectasis, cancer patients)	Comorbidities that increase the risk of infection
Intervention	Any antibiotic exposure for any infection <14 days (Prospective or retrospective)	Long-term antibiotic treatment > 2 continuous weeks	Higher probability of killing susceptible organisms and increased risk of carriage of resistant isolates
Control /comparator	Patients without antibiotic exposure		
	Patients with a different antibiotic exposure/different dose/frequency/route of administration	If there are no before-after measurement of resistance	
Outcome	Prevalence of resistance in exposed/unexposed patients	If there are not enough data available to calculate the Odds ratio of resistance in participants exposed to antibiotics compared with those without antibiotic exposure or before-after antibiotic treatment	
		Duplicate isolate reporting	
Time	Time between antibiotic exposure and isolation of resistant organisms	Studies were excluded if there are no data available on the last know antibiotic exposure	
Setting	Primary care		
	General practices		
	Outpatient clinics		
	Paediatric clinics		
	Emergency department		

Supplementary Material 5. Search strategy

PubMed
("Drug Resistance"[Mesh] OR Resistance[tiab] OR Resistant[tiab] OR Multiresistant[tiab]) AND ("Anti-Bacterial Agents"[Mesh] OR "Macrolides"[Mesh] OR "beta-Lactams"[Mesh] OR Antibacterial[tiab] OR Antibacterials[tiab] OR Antibiotics[tiab] OR Antibiotic[tiab] OR Macrolides[tiab] OR Macrolide[tiab] OR beta-Lactams[tiab] OR Antimicrobial[tiab] OR Antimicrobials[tiab] OR Penicillin[tiab] OR Methicillin[tiab] OR ampicillin[tiab] OR azithromycin[tiab] OR Cephalexin[tiab]) AND ("Population Surveillance"[Mesh] OR "Primary Health Care"[Mesh] OR "Ambulatory Care"[Mesh] OR "Outpatients"[Mesh] OR "Community-Acquired Infections"[Mesh] OR "Demography"[Mesh] OR "Carrier State"[Mesh] OR "Endemic Diseases"[Mesh] OR “Primary care”[tiab] OR “Primary healthcare”[tiab] OR “Family practice”[tiab] OR “General practice”[tiab] OR Ambulatory[tiab] OR Outpatients[tiab] OR Outpatient[tiab] OR Community[tiab] OR Communities[tiab] OR Surveillance[tiab] OR Carrier[tiab] OR Carriage[tiab] OR Area[tiab] OR Areas[tiab] OR Region[tiab] OR Regions[tiab] OR Demographic[tiab]) AND ("Drug Prescriptions"[Mesh] OR "Prescriptions"[Mesh] OR “therapeutic use“[sh] OR Prescriptions[tiab] OR Prescription[tiab] OR Prescribing[tiab] OR Prescribe[tiab] OR Prescribed[tiab] OR Consumption[tiab] OR Courses[tiab] OR Course[tiab] OR Programme[tiab] OR Programmes[tiab] OR Dose[tiab] OR Doses[tiab] OR Exposure[tiab] OR Isolates[tiab] OR Isolated[tiab] OR Risk[ti]) AND ("Patients"[Mesh] OR “Drug therapy”[sh] OR “Drug effects”[sh] OR Microbiology[sh] OR Treatment[tiab] OR Patient[tiab] OR Patients[tiab] OR Patient's[tiab]) AND (“Randomized Controlled Trial”[pt] OR “Controlled Clinical Trial”[pt] OR "Epidemiologic Studies"[Mesh] OR Randomly[tiab] OR Randomised[tiab] OR Randomized[tiab] OR Group[tiab] OR Groups[tiab] OR Control[tiab] OR Controlled[tiab] OR Case[tiab] OR Cases[tiab] OR Multicenter OR Center[tiab] OR Centre[tiab] OR Trial[tiab] OR Trials[tiab] OR Compare[tiab] OR Compared[tiab] OR Comparison[tiab] OR Cohort[tiab] OR Observed[tiab] OR Observational[tiab] OR Questionnaires[tiab] OR Questionnaires[tiab] OR Frequency[tiab] OR Frequencies[tiab] OR Baseline[tiab] OR Modeling[tiab]) NOT ("Hospitals"[Mesh] OR “Inpatients”[Mesh] OR "Cross Infection"[Mesh] OR Hospitals[ti] OR Hospital[ti] OR Inpatients[tiab] OR Inpatient[tiab] OR “Cross infection”[tiab] OR “Cross infections”[tiab] OR “Hospital acquired”[tiab] OR "Hospital infection"[tiab] OR "Hospital infections"[tiab] OR Animal[tiab] OR Animals[tiab]) NOT

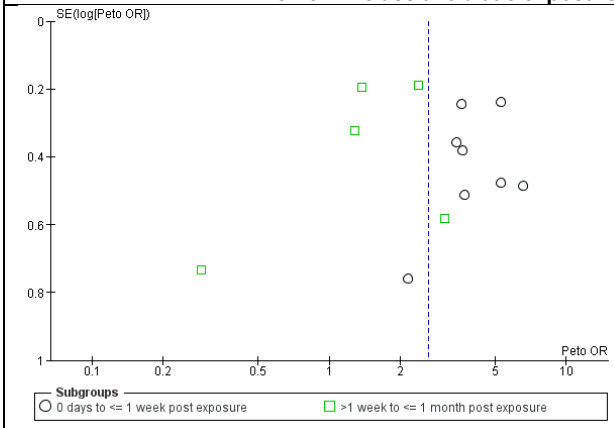
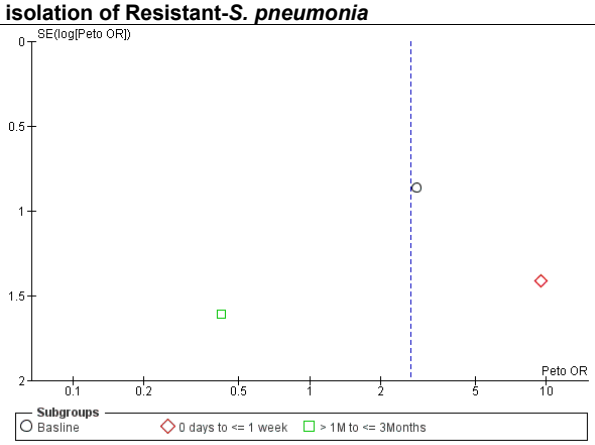
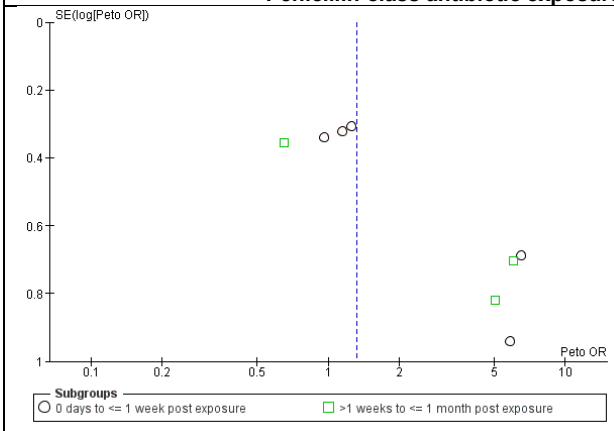
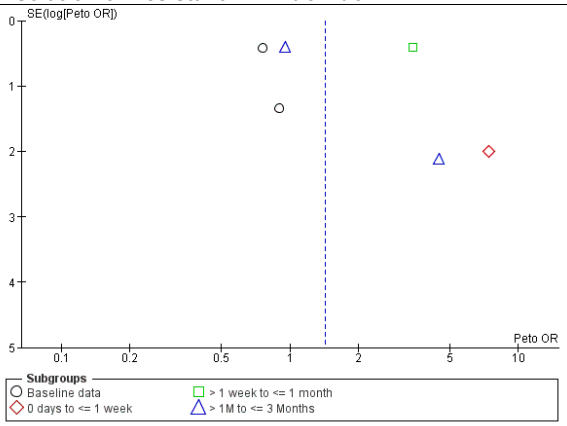
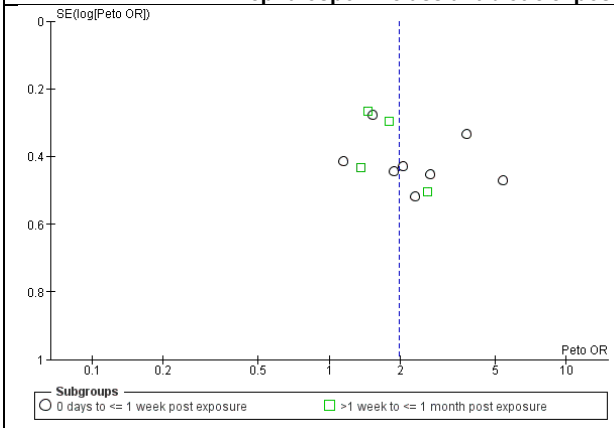
(Review[pt] OR Meta Analysis[pt] OR News[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR comment on[ti] OR systematic review[ti] or literature review[ti]) NOT (Animals[Mesh] not (Animals[Mesh] and Humans[Mesh]))
CENTRAL (Cochrane)
([mh "Drug Resistance"] OR Resistance:ti,ab OR Resistant:ti,ab OR Multiresistant:ti,ab) AND ([mh "Anti-Bacterial Agents"] OR [mh "Macrolides"] OR [mh "beta-Lactams"] OR Antibacterial:ti,ab OR Antibacterials:ti,ab OR Antibiotics:ti,ab OR Antibiotic:ti,ab OR Macrolides:ti,ab OR Macrolide:ti,ab OR beta-Lactams:ti,ab OR Antimicrobial:ti,ab OR Antimicrobials:ti,ab OR Penicillin:ti,ab OR Methicillin:ti,ab OR ampicillin:ti,ab OR azithromycin:ti,ab OR Cephalexin:ti,ab) AND ([mh “Population Surveillance"] OR [mh "Primary Health Care"] OR [mh "Ambulatory Care"] OR [mh "Outpatients"] OR [mh "Community-Acquired Infections"] OR [mh "Demography"] OR [mh "Carrier State"] OR [mh "Endemic Diseases"] OR “Primary care”:ti,ab OR “Primary healthcare”:ti,ab OR “Family practice”:ti,ab OR “General practice”:ti,ab OR Ambulatory:ti,ab OR Outpatients:ti,ab OR Outpatient:ti,ab OR Community:ti,ab OR Communities:ti,ab OR Surveillance:ti,ab OR Carrier:ti,ab OR Carriage:ti,ab OR Area:ti,ab OR Areas:ti,ab OR Region:ti,ab OR Regions:ti,ab OR Demographic:ti,ab) AND ([mh "Drug Prescriptions"] OR [mh "Prescriptions"] OR "therapeutic use":kw OR Prescriptions:ti,ab OR Prescription:ti,ab OR Prescribing:ti,ab OR Prescribe:ti,ab OR Prescribed:ti,ab OR Consumption:ti,ab OR Courses:ti,ab OR Course:ti,ab OR Programme:ti,ab OR Programmes:ti,ab OR Dose:ti,ab OR Doses:ti,ab OR Exposure:ti,ab OR Isolates:ti,ab OR Isolated:ti,ab OR Risk:ti) AND ([mh "Patients"] OR "Drug therapy":kw OR "Drug effects":kw OR Microbiology:kw OR Treatment:ti,ab OR Patient:ti,ab OR Patients:ti,ab OR Patient’s:ti,ab) NOT ([mh "Hospitals"] OR [mh "Inpatients"] OR [mh "Cross Infection"] OR Hospitals:ti OR Hospital:ti OR Inpatients:ti,ab OR Inpatient:ti,ab OR "Cross infection":ti,ab OR "Cross infections":ti,ab OR "Hospital acquired":ti,ab OR "Hospital infection":ti,ab OR "Hospital infections":ti,ab OR Animal:ti,ab OR Animals:ti,ab) NOT ([mh Animals] not ([mh Animals] and [mh Humans]))
EMBASE
('Drug Resistance'/exp OR Resistance:ti,ab OR Resistant:ti,ab OR Multiresistant:ti,ab) AND ('antibiotic agent'/exp OR 'Macrolide'/exp OR 'beta lactam'/exp OR Antibacterial:ti,ab OR Antibacterials:ti,ab OR Antibiotics:ti,ab OR Antibiotic:ti,ab OR Macrolides:ti,ab OR Macrolide:ti,ab OR beta-Lactams:ti,ab

OR Antimicrobial:ti,ab OR Antimicrobials:ti,ab OR Penicillin:ti,ab OR Methicillin:ti,ab OR ampicillin:ti,ab OR azithromycin:ti,ab OR Cephalexin:ti,ab)
AND
('health survey'/exp OR 'Primary Health Care'/exp OR 'Ambulatory Care'/exp OR 'Outpatient'/exp OR 'Community-Acquired Infection'/exp OR 'Demography'/exp OR 'heterozygote'/exp OR 'Endemic Disease'/exp OR "Primary care":ti,ab OR "Primary healthcare":ti,ab OR "Family practice":ti,ab OR "General practice":ti,ab OR Ambulatory:ti,ab OR Outpatients:ti,ab OR Outpatient:ti,ab OR Community:ti,ab OR Communities:ti,ab OR Surveillance:ti,ab OR Carrier:ti,ab OR Carriage:ti,ab OR Area:ti,ab OR Areas:ti,ab OR Region:ti,ab OR Regions:ti,ab OR Demographic:ti,ab)
AND
('Prescription'/exp OR 'Prescriptions'/exp OR Prescriptions:ti,ab OR Prescription:ti,ab OR Prescribing:ti,ab OR Prescribe:ti,ab OR Prescribed:ti,ab OR Consumption:ti,ab OR Courses:ti,ab OR Course:ti,ab OR Programme:ti,ab OR Programmes:ti,ab OR Dose:ti,ab OR Doses:ti,ab OR Exposure:ti,ab OR Isolates:ti,ab OR Isolated:ti,ab OR Risk:ti)
AND
('Patient'/exp OR Patient:ti,ab OR Patients:ti,ab OR Treatment:ti,ab)
AND
('Randomized Controlled Trial':it OR 'Controlled Clinical Trial':it OR 'epidemiology'/exp OR Randomly:ti,ab OR Randomised:ti,ab OR Randomized:ti,ab OR Group:ti,ab OR Groups:ti,ab OR Control:ti,ab OR Controlled:ti,ab OR Case:ti,ab OR Cases:ti,ab OR Multicenter OR Center:ti,ab OR Centre:ti,ab OR Trial:ti,ab OR Trials:ti,ab OR Compare:ti,ab OR Compared:ti,ab OR Comparison:ti,ab OR Cohort:ti,ab OR Observed:ti,ab OR Observational:ti,ab OR Questionnaires:ti,ab OR Questionnaires:ti,ab OR Frequency:ti,ab OR Frequencies:ti,ab OR Baseline:ti,ab OR Modeling:ti,ab)
NOT
('Hospitals'/exp OR 'Inpatients'/exp OR 'Cross Infection'/exp OR Hospitals:ti OR Hospital:ti OR Inpatients:ti,ab OR Inpatient:ti,ab OR "Cross infection":ti,ab OR "Cross infections":ti,ab OR "Hospital acquired":ti,ab OR "Hospital infection":ti,ab OR "Hospital infections":ti,ab OR Animal:ti,ab OR Animals:ti,ab)
NOT
(Review:it OR Meta Analysis:it OR News:it OR Comment:it OR Editorial:it OR Letter:it OR "comment on":ti OR "systematic review":ti OR "literature review":ti)
NOT
('animal'/exp NOT ('animal'/exp AND 'human'/exp))

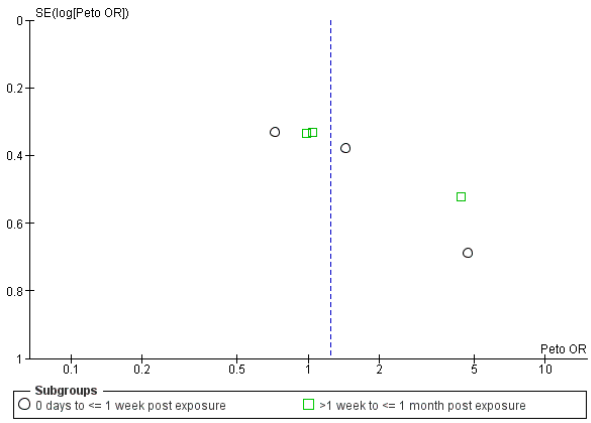
Supplementary Material 6. Detailed reasons of exclusion

Insufficient data reported	No individual patient data reported, only reporting P-value	**62**
	No data on the number of resistant isolates	**49**
	No data on the number of patients exposed to antibiotics	**47**
	Time between AB exposure and isolation of resistance not reported	**14**
	Contacted authors & no response/no full text (conf. abstract)	**23**
Ineligible participants' criteria	Hospitalised patients >50% (or hospital associated infections, inpatients)	**89**
	Patients with persistent infections/device related infections/tract abnormalities	**11**
	Immunocompromised patients	**5**
	>50% nursing home residents	**1**
	Reporting gene mutations, in-vitro resistant isolates	**5**
Ineligible exposure	Prolonged antibiotic exposure (>2 weeks of exposure)	**33**
	Pharmacokinetics of antibiotic exposure	**2**
Ineligible outcome data	No before-after outcome data in studies where all patients received antibiotic treatment	**11**
	Mixed data between resistant and susceptible isolates or all patients have resistant isolates	**7**
Ineligible study design	Case series / case reports/reviews/reports	**8**
Duplicates		**12**
Total		**379**

Supplementary Material 7. Funnel plots of comparison

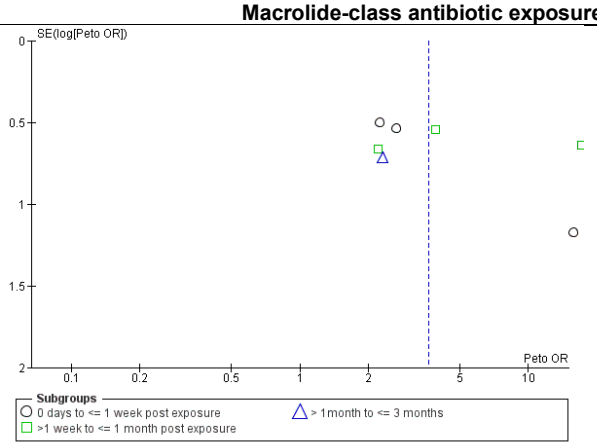
<table>
<tr><th colspan="2">Funnel plots of comparison</th></tr>
<tr><th>Studies investigating before-after antibiotic exposure (Respiratory Tract)</th><th>Studies investigating antibiotic exposure with a control group (Respiratory Tract)</th></tr>
<tr><td colspan="2">Penicillin-class antibiotic exposure and isolation of Resistant-S. pneumonia</td></tr>
<tr><td> 
</td><td> 
</td></tr>
<tr><td colspan="2">Penicillin-class antibiotic exposure and isolation of Resistant-H. influenzae</td></tr>
<tr><td> 
</td><td> 
</td></tr>
<tr><td colspan="2">Cephalosporin-class antibiotic exposure and isolation of Resistant-S. pneumonia</td></tr>
<tr><td> 
</td><td>No Data</td></tr>
</table>

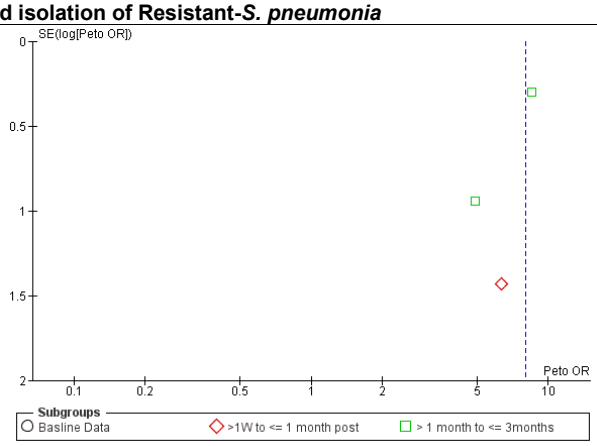
Cephalosporin-class antibiotic exposure and isolation of Resistant- *H. influenzae*



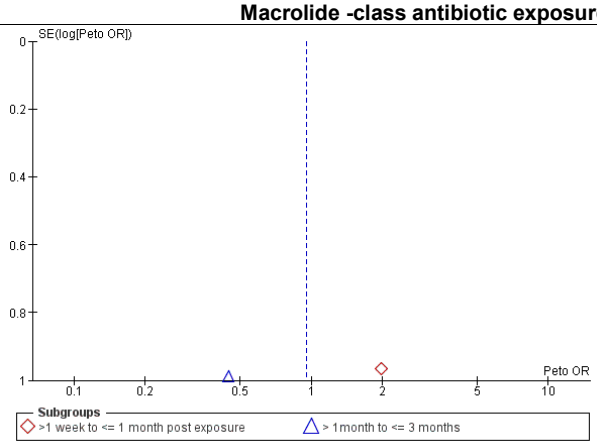
No Data

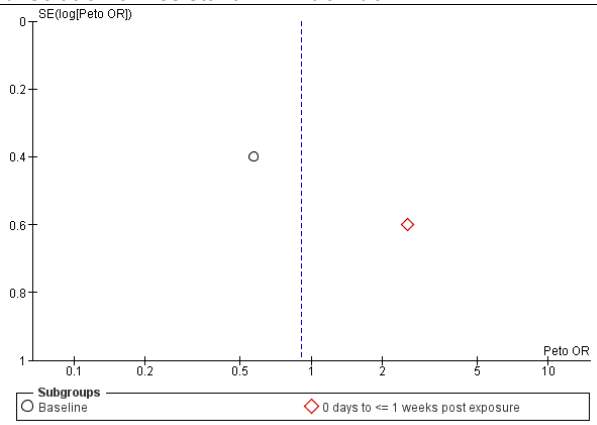
Macrolide-class antibiotic exposure and isolation of Resistant-*S. pneumonia*

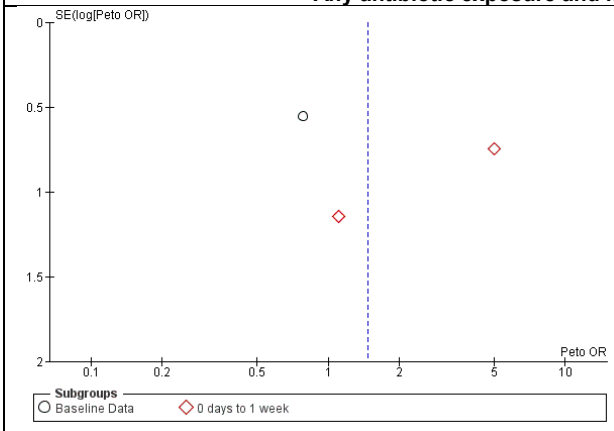
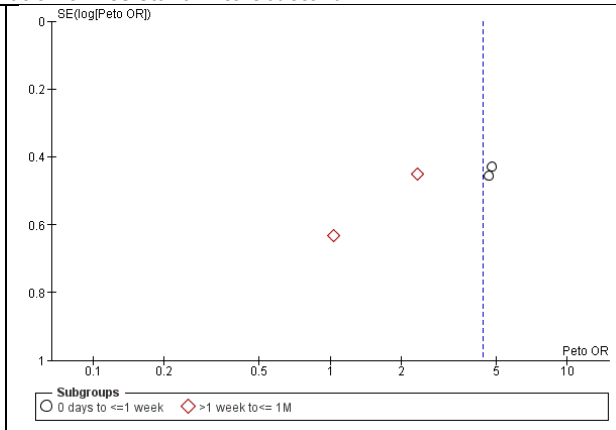




Macrolide -class antibiotic exposure and isolation of Resistant- *H. influenzae*





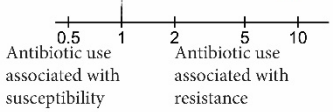
Studies investigating before-after antibiotic exposure (GIT)	**Studies investigating antibiotic exposure with a control group (GIT)**
Any antibiotic exposure and isolation of Resistant-*Enterobacteria*	
	

Supplementary Material 8. Odds ratio of resistance in other respiratory isolates post exposure to different antibiotic classes

Other Respiratory isolates **(analysis by participants)**

Exposure to any Antibiotic

Study Country/year	Bacteria	Antibiotic exposure	Antibiotic resistant to	Antibiotic exposure Exposed n N	 not-Exposed n N	Peto Odds Ratio [95% CI]
Baseline data						
USA 88	ß-lactamase producers	Penicillin	ß-lactams	3 26	3 28	1.1 [0.2, 5.9]
0 days to ≤ 1 week post exposure						
				Exposed n N	not-Exposed n N	
USA 88	ß-lactamase producers	Penicillin	ß-lactams	12 26	3 28	5.7 [1.7, 18.4]
				After n N	Before n N	
France 03 a	NGS	Telithro	Telithro	25 25	14 25	12.3 [3.3, 46.4]
France 03 b	NGS	Amoxi-clav	Amoxicillin	24 25	7 25	16.9 [5.5, 52.4]
France 99	M. catarrhalis	Amoxi-clav	ß-lactams	23 24	141 143	0.2 [0.01, 5.4]
Sweden 90 a	S. aureus	Cefaclor	ß-lactams	8 12	3 10	4.1 [0.8, 20.9]
Sweden 90 b	S. aureus	Penicillin v	ß-lactams	5 6	2 8	8.7 [1.1, 67.1]
Sweden 90 c	S. aureus	Amoxicillin	ß-lactams	16 19	5 11	6 [1.2, 29.3]
USA 09 a	S. mitis	Azi	Azi	47 50	32 49	5.8 [2.2, 15.5]
USA 09 b	S. mitis	Levo	Levo	14 18	0 45	83.8 [22.7, 308]
>1 week to ≤ 1 month post exposure						
				Exposed No Data	not-Exposed	
				After n N	Before n N	
Sweden 90 c	S. aureus	Amoxicillin	ß-lactams	17 19	5 11	8.8 [1.7, 45.9]
Sweden 90 a	S. aureus	Cefaclor	ß-lactams	6 11	3 11	2.9 [0.6, 15.5]
USA 09 a	S. mitis	Azi	Azi	45 46	32 49	8.1 [2.9, 22.6]
USA 09 b	S. mitis	Levo	Levo	2 43	0 45	7.9 [0.5, 128]
>1 month to ≤ 3 months post exposure						
				Exposed n N	not-Exposed n N	
USA 88	ß-lactamase producers	ß-lactams	Penicillin	7 26	3 28	2.9 [0.7, 11.2]
				After n N	Before n N	
France 03 a	NGS	Telithro	Telithro	22 24	14 25	6.0 [1.7, 21.1]
France 03 b	NGS	Amoxi-clav	Amoxicillin	19 24	7 25	7.5 [2.5, 22.7]
USA 09 a	S. mitis	Azi	Azi	37 39	32 49	5.6 [2.0, 15.5]
USA 09 b	S. mitis	Levo	Levo	4 41	0 45	8.8 [1.2, 64.8]



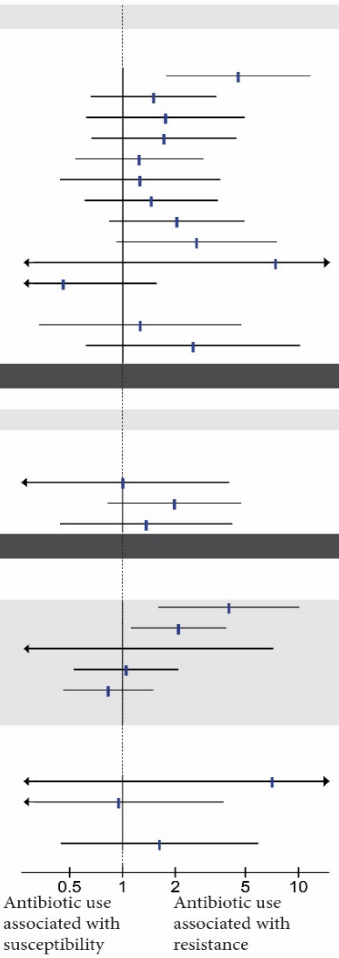
Shaded areas indicate trials with a control group
Unshaded areas indicate time-series studies (Before-after)
NGS= Nongroupable streptococci, M. catarrhalis= Moraxella catarrhalis, S. aureus = Staphylococcus aureus, S. mitis= Streptococcus mitis
Telithro=Telithromycin, Amoxi-clav=Amoxicillin-clavulanate, ß-lactams= Beta-lactams, Azi= Azithromycin, Levo=Levofloxacin

Supplementary Material 9. Co-resistance data reported among the included studies

Co-resistance data **(analysis by participants)**

Exposure to Any Antibiotic

Study Country/year	Bacteria	Antibiotic exposure	Antibiotic resistant to	Antibiotic exposure Exposed n	N	not-Exposed n	N	Peto Odds Ratio [95% CI]
0 days to ≤ 1 week post exposure								
				No Data				
				After n	N	Before n	N	
Finalnd 85 a	Enterobacteria	TMP-SMX	TMP	18	44	5	44	4.5 [1.8, 11.7]
Finland 85 b	Enterobacteria	TMP	TMP-SMX	21	43	19	49	1.5 [0.7, 3.4]
France 00 a	S. pneumoniae	Amoxicillin	Erythro	17	24	23	40	1.8 [0.6, 4.9]
France 00 b	S. pneumoniae	Amoxi-clav	Erythro	17	26	26	50	1.7 [0.7, 4.4]
France 00 c	S. pneumoniae	Cefaclor	Erythro	28	43	30	50	1.2 [0.5, 2.9]
France 00 d	S. pneumoniae	Cefuroxime	Erythro	21	29	25	37	1.3 [0.4, 3.6]
France 00 e	S. pneumoniae	Cefixime	Erythro	23	38	22	43	1.5 [0.6, 3.5]
France 00 f	S. pneumoniae	Cefpodoxime	Erythro	19	30	25	55	2.0 [0.8, 4.9]
France 00 g	S. pneumoniae	Erythro-sulf	Penicillin	13	21	15	40	5.2 [1.7, 15.8]
France 03 a	nongroupable S.	Amoxi-clav	Erythro	25	25	24	25	7.4 [0.2, 372]
France 03 b	nongroupable S.	Amoxi-clav	Telithro	16	25	20	25	0.5 [0.1, 1.6]
France 03 c	nongroupable S.	Telithro	Erythro	25	25	25	25	Not estimable
France 03 d	nongroupable S.	Telithro	Amoxicillin	6	25	5	25	1.3 [0.3, 4.7]
Spain 07	S. pneumoniae	Amoxicillin	Erythro	7	11	10	25	2.5 [0.6, 10.2]
>1 week to ≤ 1 month post exposure								
				Exposed n	N	not-Exposed n	N	
				No Data				
				After n	N	Before n	N	
Finland 85 a	Enterobacteria	TMP-SMX	TMP	4	35	5	44	1.0 [0.3, 4.0]
Finland 85 b	Enterobacteria	TMP	TMP-SMX	19	34	19	49	2 [0.8, 4.7]
Spain 07	S. pneumoniae	Amoxicillin	Erythro	11	23	10	25	1.4 [0.4, 4.2]
>1 month to ≤ 3 months post exposure								
				Exposed n	N	not-Exposed n	N	
Ethiopia 10 a	S. pneumoniae	Azithromycin	Clindamycin	16	93	4	98	4.0 [1.6, 10.1]
Ethiopia 10 b	S. pneumoniae	Azithromycin	Erythro	34	93	21	98	2.1 [1.1, 3.9]
Ethiopia 10 c	S. pneumoniae	Azithromycin	Penicillin	0	93	1	98	0.1 [0.0, 7.2]
Nepal 05 a	S. pneumoniae	Azithromycin	Tetracycline	28	163	15	91	1.1 [0.5, 2.1]
Nepal 05 b	S. pneumoniae	Azithromycin	TMP-SMX	39	163	25	91	0.8 [0.5, 1.5]
Nepal 05 c	S. pneumoniae	Azithromycin	Penicillin	0	163	0	91	Not estimable
				After n	N	Before n	N	
France 03 a	nongroupable S.	Amoxi-clav	Erythro	24	24	24	25	7.1 [0.1, 358]
France 03 b	nongroupable S.	Amoxi-clav	Telithro	19	24	20	25	1 [0.2, 3.8]
France 03 d	nongroupable S.	Telithro	Erythro	24	24	25	25	Not estimable
France 03 e	nongroupable S.	Telithro	Amoxicillin	7	24	5	25	1.6 [0.5, 5.9]



Shaded areas indicate trials with a control group
Unshaded areas indicate time-series studies (Before-after)
TMP= Trimethorprim, TMP-SMX= Trimethoprim-sulfamethoxazole,
Erthro=Erythromycin, Erthro-sulf= Erythromycin-sulfizoxazole, Telithro=Telithromycin, Amoxi-clav=Amoxicillin-clavulanate
*Data could not be extracted from 3 studies

Chapter 6

Theme 3b: Reporting quality of antibiotic resistance studies

An analysis of reporting quality of prospective studies examining community antibiotic use and resistance.

Mina Bakhit, Chris Del Mar, Anna Mae Scott, Tammy Hoffmann

Trials 2018 **19**:656 https://doi.org/10.1186/s13063-018-3040-6

Preamble

The previous study discovered that the quality of how resistance data were analysed and reported was poor in some studies. This contributed to the uncertainty of the review's estimates. Although the number of studies examining antibiotic resistance is rapidly increasing, an examination of the completeness of reporting in prospective studies investigating antibiotic resistance had not occurred. Exploring the problem of reporting in a specific content area is often done as a way of seeing if an adapted or new reporting guideline is needed to assist authors and peer reviewers. This study (Study 4) is the first step towards facilitating for better reporting of prospective studies of antibiotic resistance.

This chapter consists of the paper titled "*An analysis of reporting quality of prospective studies examining community antibiotic use and resistance.*", published in *Trials* journal. It explores the reporting quality of antibiotic resistance in prospective primary studies that examined antibiotic use and resistance.

Abstract

Background—Antibiotic resistance is a global problem, but the relationship between antibiotic use and resistance development and decay is not well understood. This knowledge is best provided by prospective studies, but to be useful they must be both conducted and reported well. Little is known about the reporting quality of these studies. This study aimed to assess the quality of reporting in prospective studies which investigated antibiotic resistance following antibiotic exposure in community-based individuals.

Methods—The quality of reporting of prospective studies (17 randomised trials, 8 cohort studies) identified in a systematic review of the relationship between antibiotic use and resistance were assessed independently by two researchers using checklists (one for trials, one for cohort studies) developed from existing reporting guidelines for these designs and this field.

Results—The mean percentage (SD, minimum-maximum) of mandatory items that were adequately described by the included studies was 59% for trials (14%, 36%–84%) and 52% for cohort studies (17%, 13%–70%). Most studies adequately described the study background and rationale, the type, combination, and duration of the antibiotic intervention, and the sampling procedures followed to isolate resistant bacteria. Most studies did not report the incident numbers of resistant and susceptible isolates analysed at each time-point. Blinding and sample size calculation was inadequately reported in almost half of the trials and all cohort studies.

Conclusions—The quality of reporting in prospective studies investigating the association between antibiotic exposure in the community and isolation of resistance isolates is variable. Some details were missing in over half of the studies, which precludes a complete risk of bias assessment and accurate interpretation and synthesis of results.

Background

Antibiotic resistance is a global public health concern, threatening lives by jeopardising successful treatment of a vast range of bacterial infections (1, 2). It is estimated that 10 million people may die in 2050 because of resistance (3). Antibiotic prescribing levels in primary care are high (4, 5), even though for many of the conditions for which they are prescribed (such as acute respiratory infections), antibiotics provide minimal benefits, and these may not be outweighed by the harms of their use (6-10).

Antibiotic use drives resistance (11-13) and there is some indication that resistance decays over time (13). Knowledge about the association between antibiotic use, the development of resistance, and timeframes of potential decay is important for informing public health messages, antibiotic resistance campaigns, and clinician training. However, evidence syntheses investigating the relationship between antibiotic exposure and the development and decay of resistance have been limited to two systematic reviews which have included mostly studies with retrospective designs (11, 12). Understanding the association between antibiotic exposure and isolation of resistance bacteria is best informed by prospective study designs. Such designs offer better opportunities to control for confounding factors, including more precise time frames of the duration between antibiotic exposure and isolation of resistance bacteria which helps to avoid the uncertainty that is implicit in 'time-until' periods that are dictated by retrospective designs. As global concern about resistance increases, an increasing number of prospective studies investigating this issue are being conducted.

However, to provide interpretable evidence and enable complete risk of bias assessment, these studies need to be reported clearly and comprehensively. There are characteristics of studies that measure antibiotic exposure and resistance which are not adequately captured by existing reporting checklists and researchers may not have adequate awareness of these issues and guidance about how to report such studies. We are not aware of any studies which have examined the quality of reporting of studies about antibiotic use and resistance.

We aimed to assess the completeness of reporting of prospective primary studies that examined antibiotic use and resistance.

Methods

Selection of included studies

Studies were included in this study if they had been identified as part of a recently published systematic review which assessed the extent of bacterial resistance in individuals caused by antibiotic use in primary care, and the rate of decay of resistance (13).

Full details of the systematic review search are available elsewhere (13). Briefly, we searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from inception until the first week of May 2017, using MeSH terms, keywords, and forward and backward citation searches. We included randomised controlled trials and prospective cohort studies which compared antibiotic-exposed patients in the community against controls. Our outcome was the prevalence of resistance bacteria over time.

Assessment of the quality of reporting of included studies

For the present study, we developed two assessment checklists (one for trials and one for prospective cohort studies), based on existing reporting guidelines relevant to these study designs and this field. For trials, the relevant guideline was the Consolidated Standards of Reporting Trials statement (CONSORT) (14); for cohort studies, the relevant guidelines were Strengthening the Reporting of Observational studies in Epidemiology (STROBE) (15) and its extension for optimising reporting of epidemiological studies in Antimicrobial Stewardship (STROBE-AMS) (16). Additional reporting recommendations that are relevant to both study types include the Template for Intervention Description and Replication (TIDieR (17)) items and those specific to resistance reporting in systematic reviews of antibiotic interventions (18).

Informed by our experience from completing the systematic review, several items necessary for the accurate interpretation of results were added to the checklists. The resultant checklists were piloted with 4 epidemiologists and 4 antibiotic resistance researchers who used them to assess the quality of reporting of a

small number of eligible studies. Following this, minor modifications were made to the grouping of the items, and the explanatory wording of some of the additional items. The final version of trial checklist had 89 items and the cohort checklist had 81 items.

Two researchers (MB and AMS) then used the checklists to independently assess the quality of reporting of each included study. Each item was rated *Yes* (if the study adequately described the item), *No* (if it did not), or *Not applicable*. Agreement between assessors was reached through discussion after small batches of 5 studies were rated, and discrepancies resolved through discussion with a third researcher (TH or CDM). The agreement between the two assessors was not calculated. The complete checklists with item descriptions and the source of each item are available in Supplementary Materials 10 and 11.

Data analysis

Data were analysed using Microsoft Excel® 2016 and descriptive statistics were calculated.

Results

The sample of articles consisted of 17 randomised controlled trials and 8 prospective cohort studies. The trials primarily assessed the risk of isolation of post-treatment carriage of resistant bacteria. They were published from 1982 to 2016 and conducted in 10 countries. The cohort studies assessed changes in resistance patterns before and after antibiotic use. They were published from 1988 to 2008 and from 7 countries (the full list of included articles is shown in Supplementary Material 12).

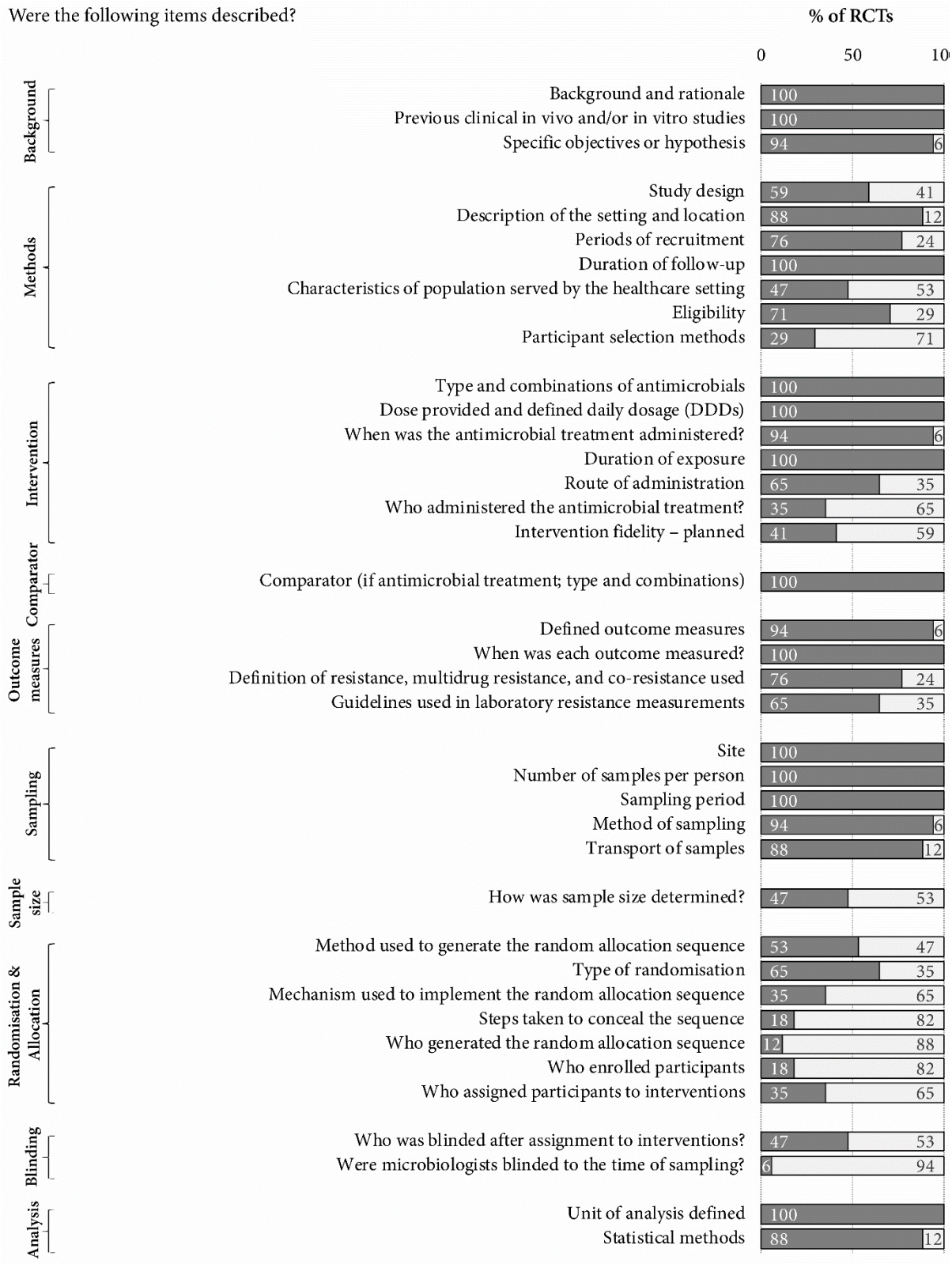
Completeness of reporting - trials

For the 17 trials, 70 mandatory items and an additional 19 'if applicable' items were scored. Twelve (17%) mandatory items were reported by all trials; one item (describing other organisms susceptible to the exposed antimicrobial or same class) was not reported by any trials. The mean percentage (SD, minimum-maximum) of the mandatory items that were adequately described by the trials was 59% (14%, 36%–84%) (Fig. 10). Supplementary Material 13 shows the percentages of trials that adequately described each item including the ‘if

applicable' items and Supplementary Material 14 shows the percentage of items adequately described by each trial.

The items that were most commonly reported include those about: *study background (*all trials provided the study rationale and described any previous in vivo and/or in vitro studies); *intervention (*most trials adequately described the type of antibiotics, duration and dose); and *sampling (*almost all trials adequately reported the sampling procedures followed for isolating resistant isolates including the site, number of samples per person, and sampling period).

Items that were poorly reported by many trials include those describing the sample size, randomisation, blinding, and the results. Almost half of the trials reported the sample size determination, and over half of the trials poorly described the methods used for randomisation and allocation (including the person/s responsible for generating the random allocation sequence, and the steps taken to conceal the randomisation sequence). Blinding reporting was incomplete in almost half of the trials and only one study reported blinding of microbiologists to the time of sampling. Many items describing the results were missing in the majority of the trials, including key details such as: the numbers analysed at nominated time-points, particularly the number of isolates susceptible to the intervention or comparator (if applicable); and the number of participants with sterile swabs (clean-catch swabs) or resistance /susceptibility among other organisms (other than the index pathogen) isolated from other body site (other than the system/site of interest).


Were the following items described?
% of RCTs
0
50
10
Background
Background and rationale 100
Previous clinical in vivo and/or in vitro studies 100
Specific objectives or hypothesis 94 6
Methods
Study design 59 41
Description of the setting and location 88 12
Periods of recruitment 76 24
Duration of follow-up 100
Characteristics of population served by the healthcare setting 47 53
Eligibility 71 29
Participant selection methods 29 71
Intervention
Type and combinations of antimicrobials 100
Dose provided and defined daily dosage (DDDs) 100
When was the antimicrobial treatment administered? 94 6
Duration of exposure 100
Route of administration 65 35
Who administered the antimicrobial treatment? 35 65
Intervention fidelity – planned 41 59
Comparator
Comparator (if antimicrobial treatment; type and combinations) 100
Outcome measures
Defined outcome measures 94 6
When was each outcome measured? 100
Definition of resistance, multidrug resistance, and co-resistance used 76 24
Guidelines used in laboratory resistance measurements 65 35
Sampling
Site 100
Number of samples per person 100
Sampling period 100
Method of sampling 94 6
Transport of samples 88 12
Sample size
How was sample size determined? 47 53
Randomisation & Allocation
Method used to generate the random allocation sequence 53 47
Type of randomisation 65 35
Mechanism used to implement the random allocation sequence 35 65
Steps taken to conceal the sequence 18 82
Who generated the random allocation sequence 12 88
Who enrolled participants 18 82
Who assigned participants to interventions 35 65
Blinding
Who was blinded after assignment to interventions? 47 53
Were microbiologists blinded to the time of sampling? 6 94
Analysis
Unit of analysis defined 100
Statistical methods 88 12

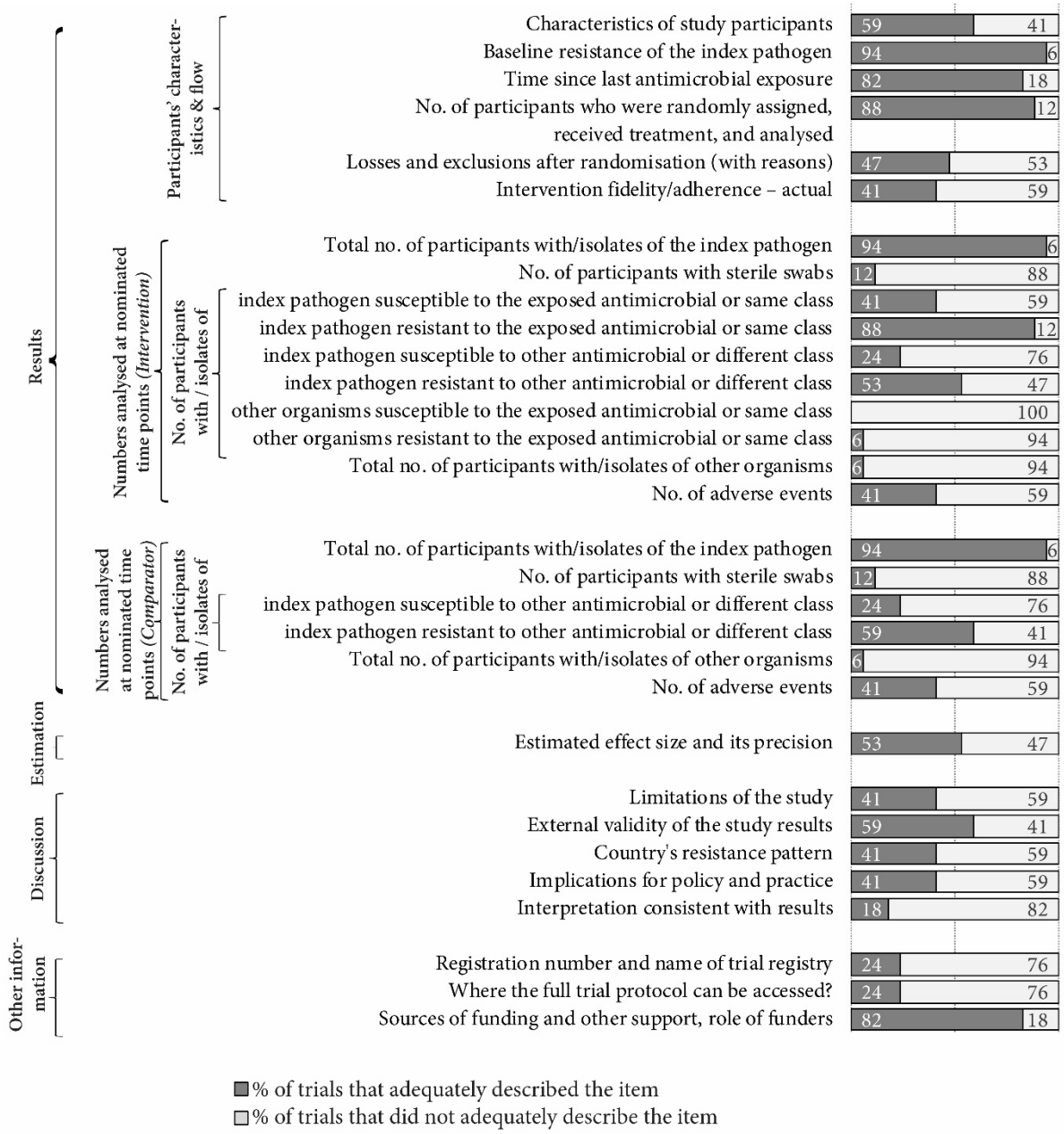
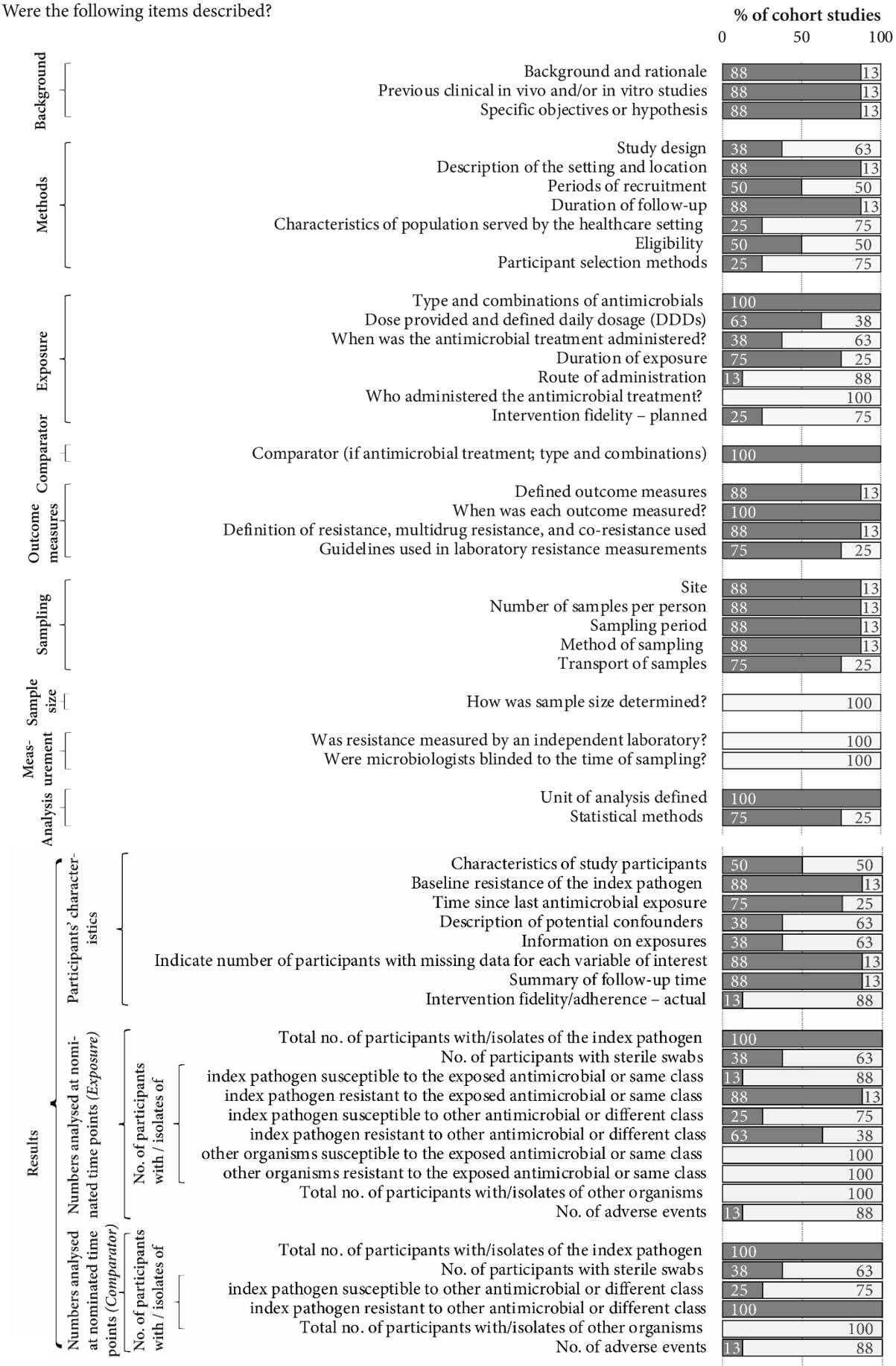


Fig. 10. Quality of reporting, % of RCTs meeting each ***item*** (studies= 17, mandatory items =70)

Completeness of reporting - Cohort studies

In the 8 cohort studies, 63 mandatory items and an additional 19 'if applicable' items were scored: 7 (11%) mandatory items were reported by all cohort studies; 8 (13%) were not reported by any. The mean percentage (SD, minimum-maximum) of the mandatory items that were adequately described by the studies was 52% (17%, 13%– 70%) (Fig. 11). Supplementary Material 15 shows the percentage of cohort studies that adequately described each item including the 'if applicable' items and Supplementary Material 16 shows the percentage of items adequately described by each study.

The items most commonly reported were those about the: *study background (*most described specific objectives and study rationale); *outcome measures* (most defined each measure and reported when each was measured); and *sampling (*most studies adequately described the sampling procedures used, including the site, number of samples per person, and sampling period). Items that were poorly reported were those describing the sample size, measurement and results. None of the studies reported how their sample size was determined and none reported if resistance was measured by an independent laboratory or if the microbiologists were blinded. As with the trials, many key details about the numbers analysed were missing, such as the number of susceptible isolates to antibiotic exposure analysed at each of the nominated time-points, along with the resistance/susceptibility among other organisms isolated from another body site.


Were the following items described?
% of cohort studies
0
50
100
Background
Background and rationale 88 13
Previous clinical in vivo and/or in vitro studies 88 13
Specific objectives or hypothesis 88 13
Methods
Study design 38 63
Description of the setting and location 88 13
Periods of recruitment 50 50
Duration of follow-up 88 13
Characteristics of population served by the healthcare setting 25 75
Eligibility 50 50
Participant selection methods 25 75
Exposure
Type and combinations of antimicrobials 100
Dose provided and defined daily dosage (DDDs) 63 38
When was the antimicrobial treatment administered? 38 63
Duration of exposure 75 25
Route of administration 13 88
Who administered the antimicrobial treatment? 100
Intervention fidelity – planned 25 75
Comparator
Comparator (if antimicrobial treatment; type and combinations) 100
Outcome measures
Defined outcome measures 88 13
When was each outcome measured? 100
Definition of resistance, multidrug resistance, and co-resistance used 88 13
Guidelines used in laboratory resistance measurements 75 25
Sampling
Site 88 13
Number of samples per person 88 13
Sampling period 88 13
Method of sampling 88 13
Transport of samples 75 25
Sample size
How was sample size determined? 100
Meas-urement
Was resistance measured by an independent laboratory? 100
Were microbiologists blinded to the time of sampling? 100
Analysis
Unit of analysis defined 100
Statistical methods 75 25
Results
Participants' character-istics
Characteristics of study participants 50 50
Baseline resistance of the index pathogen 88 13
Time since last antimicrobial exposure 75 25
Description of potential confounders 38 63
Information on exposures 38 63
Indicate number of participants with missing data for each variable of interest 88 13
Summary of follow-up time 88 13
Intervention fidelity/adherence – actual 13 88
Numbers analysed at nomi-nated time points (Exposure)
Total no. of participants with/isolates of the index pathogen 100
No. of participants with sterile swabs 38 63
No. of participants with / isolates of
index pathogen susceptible to the exposed antimicrobial or same class 13 88
index pathogen resistant to the exposed antimicrobial or same class 88 13
index pathogen susceptible to other antimicrobial or different class 25 75
index pathogen resistant to other antimicrobial or different class 63 38
other organisms susceptible to the exposed antimicrobial or same class 100
other organisms resistant to the exposed antimicrobial or same class 100
Total no. of participants with/isolates of other organisms 100
No. of adverse events 13 88
Numbers analysed at nominated time points (Comparator)
Total no. of participants with/isolates of the index pathogen 100
No. of participants with sterile swabs 38 63
No. of participants with / isolates of
index pathogen susceptible to other antimicrobial or different class 25 75
index pathogen resistant to other antimicrobial or different class 100
Total no. of participants with/isolates of other organisms 100
No. of adverse events 13 88

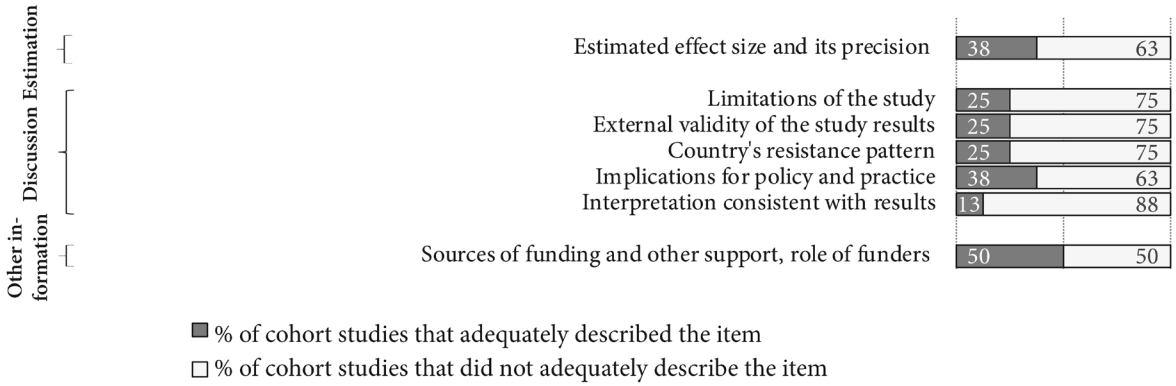


Fig. 11. Quality of reporting, % of Cohort studies meeting each ***item*** (studies= 8, mandatory items =63)

Discussion

The quality of reporting of prospective studies examining antibiotic use and resistance varied in this study. Some aspects of the studies (such as the sampling procedures used and rationale for the study) were described in most, but some details were missing in many studies. Some of the missing items, such as those about blinding or the numbers analysed, are particularly important for assessing a study's risk of bias and interpreting its results accurately.

Few studies reported the incident numbers of both resistant and susceptible isolates analysed at each time-point (and for both the intervention and/or comparator groups), and only one study reported the isolation of resistant isolates from body sites other than the target site/system. This may be as important to know as the resistance in the originally infected site, from the point of view of antibiotic resistance generation in the microbiome, and hence in the community at large. Similarly, most studies only reported resistance to the class of antibiotic used, although some studies also reported resistance to other antibiotic classes – a possibly important omission because of induced co-resistance to antibiotics from different classes (19).

Reporting of how and whether blinding occurred was inadequate in almost half of the studies. Only one study reported whether the microbiologist was blinded to the time of sampling. Data on changes in resistance over time could be biased if those responsible for measuring resistance are not blinded to the time of sampling. As with other aspects of methods reporting, if a study does not describe a process, a reader cannot be sure if the process did not occur or was just not reported. This uncertainty impedes risk of bias assessment and decreases the confidence in the reported results.

While describing a study with sufficient detail to enable replication and interpretation of results is good scientific practice, many authors are not aware of all the details that need to be reported to sufficiently describe a study. To assist authors with comprehensively describing studies, reporting guidelines have been developed. However, for our sample of included studies, the impact of reporting guidelines would have been minimal, as most (88%) of the included cohort studies were published before the release of the STROBE reporting guidelines

(and all before the STROBE-AMS publication), and all but one of the included trials were published before the 2010 CONSORT statement, although most (except 3) were published before the 1996 CONSORT statement (20).

As our sample of studies is limited to those included in a systematic review of antibiotic resistance in individuals who were prescribed antibiotics in primary care, this may limit the generalisability of results beyond this setting. Additionally, the checklists used to assess the studies were modified from existing checklists and informed by the pragmatic experience of researchers assessing and synthesising these types of studies – the modified checklist have not been formally assessed. However, a strength of this study is the independent assessment of the included studies by two authors.

Conclusion

In this study of the reporting quality of prospective studies examining antibiotic use and resistance, just over half of the mandatory checklist items were adequately described for the randomised trials and cohort studies included. Some items (such as the type, combination, and duration of the antibiotic intervention, and the sampling procedures used to isolate resistant bacteria) were adequately described by most studies, whereas other details (such as the incident numbers of resistant and susceptible isolates analysed at each time-point) were not described by most. Improving the quality of reporting of future studies which measure antibiotic resistance is necessary to aid accurate synthesis and interpretation of results. Better reporting may be facilitated by a reporting checklist, which is created following the recommendations for developing reporting guidelines (21), that is specific to prospective studies of antibiotic use and resistance. This will help to improve the quality of reporting available to the research community, clinicians, and policy makers.

Declarations

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no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions: MB, CDM, and TH designed the study. MB and AMS performed data extraction and quality assessment. MB analysed the data and designed the figures. MB drafted the original manuscript and AMS, TH and CDM contributed to writing and revising the manuscript. All authors revised and approved the final manuscript.

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Competing interests: The authors declare that they have no competing interests.

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Supplementary material

Published with article presented in Chapter 6 (Study 4)

https://doi.org/10.1186/s13063-018-3040-6

Supplementary Material 10. Checklist used to assess RCTs and source of each item. https://doi.org/10.6084/m9.figshare.7391855.v1

Were the following items described?		**Source of item**
Background		
	Background and explanation of rationale and theory	STROBE/CONSORT
	Reported previous clinical ***in vivo*** and/or ***in vitro*** studies	STROBE-AMS
	Specific ***objectives*** or ***hypothesis***	STROBE/CONSORT
Methods		
	Study design ***described***	STROBE/CONSORT
	Description of the ***setting*** (e.g. hospital, Emergency department, etc.) and ***location*** (e.g. city, region, country)	STROBE-AMS/STROBE/CONSORT
	Periods of ***recruitment***	STROBE
	Duration of ***follow-up***	STROBE
	Characteristics of ***population served*** by the healthcare setting where patients were recruited e.g. urban/rural, low socioeconomic status	STROBE-AMS
	Eligibility criteria (e.g. inclusion & exclusion criteria)	STROBE/CONSORT
	Participant ***selection methods***	STROBE
Description of intervention / exposure	Type and combinations of antimicrobials ***(What)*** (e.g. Amoxicillin, Amoxicillin-clavulanic, etc.)	STROBE-AMS
	Dose ***(How much)*** (e.g. 500 mg)	STROBE-AMS
	When was the antimicrobial treatment administered? (e.g. 3 times/day, in the morning, after food)	TIDieR/CONSORT
	Is dose provided as defined daily dosage ***(DDDs)***?	STROBE-AMS
	If not, ***other measurement used*** with justification (e.g. packages, prescriptions)	STROBE-AMS
	Duration of exposure ***(How long)*** (e.g. 7 days)	STROBE-AMS
	Route of administration ***(Mode of delivery)*** (e.g. oral, ointment, etc.)	STROBE-AMS
	Rationale for ***grouping*** of antimicrobials (if applicable)	STROBE-AMS
	Who administered the antimicrobial treatment? (e.g. researcher, clinicians, nurses)	TIDieR
	Was the intervention planned to be ***personalised, or titrated***? (personalised doses by body weight, route specific administration, age, excipient)	TIDieR
	If so, was the what, why, when, and how of it described?	TIDieR
	Intervention fidelity – planned: How, and when antimicrobial consumption data were obtained (e.g. pharmacy record, patients' diary to be filled in daily, etc.)	TIDieR
Description of comparator (if applicable)	Type and combinations of antimicrobials ***(What)*** (e.g. Amoxicillin, Amoxicillin-clavulanic, etc.)	STROBE-AMS
	Dose ***(How much)*** (e.g. 500 mg)	STROBE-AMS
	When was the antimicrobial treatment administered? (e.g. 3 times/day, in the morning, after food)	TIDieR/CONSORT
	Is dose provided as defined daily dosage (***DDDs***)?	STROBE-AMS
	If not, ***other measurement used*** with justification (e.g. packages, prescriptions)	STROBE-AMS
	Duration of exposure ***(How long)*** (e.g. 7 days)	STROBE-AMS
	Route of administration ***(Mode of delivery)*** (e.g. Oral, ointment, etc.)	STROBE-AMS
	Rationale for ***grouping*** of antimicrobials (if applicable)	STROBE-AMS
	Who administered the antimicrobial treatment? (e.g. researcher, clinicians, nurses)	TIDieR
	Was the intervention planned to be ***personalised, or titrated***? (personalised doses by body weight, route specific administration, age, excipient)	TIDieR
	If so, was the what, why, when, and how of it described?	TIDieR
	Comparator fidelity – planned: How, and when antimicrobial consumption data were obtained (e.g. pharmacy record, patients' diary to be filled in daily, etc.)	TIDieR
Outcome measures	Defined pre-specified ***primary and secondary*** outcome measures	CONSORT
	When was each outcome measured?	CONSORT
	Definition of ***infection*** or ***colonisation*** used. If new definition, then evidence of robustness of the new definition	STROBE-AMS
	Definition of ***resistance*** (e.g. MIC values, cut-off points), multidrug resistance, and co-resistance used	STROBE-AMS

	Guidelines used in laboratory resistance measurements (NCCLS/CLSI, EUCAST, National German standards, etc.)	Added Item
Sampling: -	***site***	Added Item
	number of samples per person	Added Item
	sampling ***period***	Added Item
	method of sampling (e.g. midstream urine catch)	Added Item
	transport of samples (e.g. transport medium)	Added Item
Sample size	How was ***sample size*** determined?	STROBE/CONSORT
Randomisation and allocation	Method used to ***generate*** the ***random allocation*** sequence	CONSORT
	Type of randomisation	CONSORT
	Mechanism used to ***implement*** the random allocation sequence	CONSORT
	Any steps were taken to ***conceal*** the sequence	CONSORT
Implementation	***Who generated*** the random allocation sequence	CONSORT
	Who enrolled participants	CONSORT
	Who assigned participants to interventions	CONSORT
Blinding	***Who was blinded*** after assignment to interventions? (e.g., participants, care providers, those assessing outcomes)	CONSORT
	How did blinding occur?	CONSORT
	If no blinding occurred, was resistance measured by an ***independent laboratory***?	Added Item
	Were ***microbiologists*** blinded to the ***time of sampling***?	Added Item
Analysis	***Unit of analysis*** defined (isolates, participants, other)	STROBE-AMS
	Statistical methods used to compare groups for primary and secondary outcomes	STROBE/CONSORT
	Methods for additional analyses, such as ***subgroup analyses*** (e.g., by class of antibiotic exposure) and ***adjusted analyses***	CONSORT/STROBE-AMS
Results		
Participants' characteristics and flow	Give ***characteristics*** of study participants (e.g., demographic, clinical, social)	STROBE/CONSORT
	Baseline resistance of the index pathogen	Added Item
	Time since ***last antibiotic exposure***	Added Item
	For each group, ***number of participants*** who were randomly assigned, received intended treatment, and were analysed for the primary outcome	CONSORT
	For each group, ***losses and exclusions*** after randomisation, together with reasons	CONSORT
	Intervention fidelity/adherence – actual: the extent to which the antimicrobial was actually used or dispensed	TIDieR
Numbers analysed (Intervention)	Incident ***total number*** of participants with/isolates of the ***index pathogen*** at nominated time points	Added Item
	Number of participants not carrying the index pathogen (i.e. ***sterile swabs***) at each time point	Added Item
	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***susceptible*** to the ***exposed antimicrobial or same class*** included in each analysis	Added Item
	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***resistant*** to the ***exposed antimicrobial or same class*** included in each analysis	Added Item
	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***susceptible*** to ***other antimicrobial or different class*** (Co-resistance data) included in each analysis	Added Item
	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***resistant*** to ***other antimicrobial or different class*** (Co-resistance data) included in each analysis	Added Item
	Incident number of participants with/isolates of ***other organisms*** at nominated time points ***susceptible*** to the ***exposed antimicrobial or same class*** (from other body sites e.g., bowel, nasopharynx, skin) included in each analysis	Added Item
	Incident number of participants with/isolates of ***other organisms*** at nominated time points ***resistant*** to the exposed antimicrobial or same class (from other body sites e.g., bowel, nasopharynx, skin) included in each analysis	Added Item

	Incident ***total number*** of participants with/isolates of ***other organisms*** at nominated time points (from other body sites e.g., bowel, nasopharynx, skin) included in each analysis	Added Item
	Number of ***adverse events*** occurred during antibiotic treatment reported (nausea, rash, diarrhoea, superinfections, etc.)	CONSORT
Numbers analysed (comparator) if applicable	Incident ***total number*** of participants with/isolates of the ***index pathogen*** at nominated time points	Added Item
	Number of participants not carrying the index pathogen (i.e. ***sterile swabs***) at each time point	Added Item
	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***susceptible*** to the ***exposed antimicrobial or same class*** included in each analysis	Added Item
	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***resistant*** to the ***exposed antimicrobial or same class*** included in each analysis	Added Item
	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***susceptible*** to ***other antimicrobial or different class*** (Co-resistance data) included in each analysis	Added Item
	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***resistant*** to ***other antimicrobial or different class*** (Co-resistance data) included in each analysis	Added Item
	Incident number of participants with/isolates of ***other organisms*** at nominated time points ***susceptible*** to the ***exposed antimicrobial or same class*** (from other body sites e.g., bowel, nasopharynx, skin) included in each analysis	Added Item
	Incident number of participants with/isolates of ***other organisms*** at nominated time points ***resistant*** to the ***exposed antimicrobial or same class*** (from other body sites e.g., bowel, nasopharynx, skin) included in each analysis	Added Item
	Incident ***total number*** of participants with/isolates of ***other organisms*** at nominated time points (from other body sites e.g., bowel, nasopharynx, skin) included in each analysis	Added Item
	Number of ***adverse events*** occurred during antibiotic treatment reported (nausea, rash, diarrhoea, superinfections, etc.)	CONSORT
	Comparator fidelity/adherence – actual: The extent to which the antimicrobial was actually used or dispensed (if applicable)	TIDieR
Estimation	For each ***primary and secondary outcome***, and the estimated effect size and its precision (such as 95% confidence interval) (if applicable)	CONSORT
	Results of any ***other analysis*** performed, including ***subgroup analysis*** (by type of patients, type of microorganism, by class of antibiotic exposure)	STROBE/CONSORT/STROBE-AMS
Discussion		
	Limitations of the study, taking into account sources of potential bias or imprecision (both direction and magnitude of any potential bias)	STROBE/CONSORT
	Discuss study setting, type of hospital, local epidemiology for ***generalisability*** (external validity) of the study results	STROBE/CONSORT/STROBE-AMS
	Country's resistance pattern	Added Item
	If resistance-related outcomes are different between the comparison groups, discuss the implications for policy and practice	Added Item
	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence (if applicable)	CONSORT
Other information	***Registration number*** and name of trial registry	CONSORT
	Where the ***full trial protocol*** can be accessed?	CONSORT
	Sources of ***funding*** and other support (such as supply of drugs), role of funders	STROBE/CONSORT

Supplementary Material 11. Checklist used to assess cohort studies and source of each item. https://doi.org/10.6084/m9.figshare.7391864.v1

Were the following items described?		**Source of item**
Background		
	Background and explanation of rationale and theory	STROBE/CONSORT
	Reported previous clinical ***in vivo*** and/or ***in vitro*** studies	STROBE-AMS
	Specific ***objectives*** or ***hypothesis***	STROBE/CONSORT
Methods		
	Study design ***described***	STROBE/CONSORT
	Description of the ***setting*** (e.g. hospital, Emergency department, etc.) and ***location*** (e.g. city, region, country)	STROBE-AMS/STROBE/CONSORT
	Periods of ***recruitment***	STROBE
	Duration of ***follow-up***	STROBE
	Characteristics of ***population served*** by the healthcare setting where patients were recruited e.g. urban/rural, low socioeconomic status	STROBE-AMS
	Eligibility criteria (e.g. inclusion & exclusion criteria)	STROBE/CONSORT
	Participant ***selection methods***	STROBE
Description of exposure	Type and combinations of antimicrobials ***(What)*** (e.g. Amoxicillin, Amoxicillin-clavulanic, etc.)	STROBE-AMS
	Dose ***(How much)*** (e.g. 500 mg)	STROBE-AMS
	When was the antimicrobial treatment administered? (e.g. 3 times/day, in the morning, after food)	TIDieR/CONSORT
	Is dose provided as defined daily dosage ***(DDDs)***?	STROBE-AMS
	If not, ***other measurement used*** with justification (e.g. packages, prescriptions)	STROBE-AMS
	Duration of exposure ***(How long)*** (e.g. 7 days)	STROBE-AMS
	Route of administration ***(Mode of delivery)*** (e.g. oral, ointment, etc.)	STROBE-AMS
	Rationale for ***grouping*** of antimicrobials (if applicable)	STROBE-AMS
	Who administered the antimicrobial treatment? (e.g. researcher, clinicians, nurses)	TIDieR
	Was the antimicrobial exposure planned to be ***personalised, or titrated***? (personalised doses by body weight, route specific administration, age, excipient)	TIDieR
	If so, was the what, why, when, and how of it described?	TIDieR
	fidelity – planned: How, and when antimicrobial consumption data were obtained (e.g. pharmacy record, patients' diary to be filled in daily, etc.)	TIDieR
Description of comparator (if applicable)	Type and combinations of antimicrobials ***(What)*** (e.g. Amoxicillin, Amoxicillin-clavulanic, etc.)	STROBE-AMS
	Dose ***(How much)*** (e.g. 500 mg)	STROBE-AMS
	When was the antimicrobial treatment administered? (e.g. 3 times/day, in the morning, after food)	TIDieR/CONSORT
	Is dose provided as defined daily dosage (***DDDs***)?	STROBE-AMS
	If not, ***other measurement used*** with justification (e.g. packages, prescriptions)	STROBE-AMS
	Duration of exposure ***(How long)*** (e.g. 7 days)	STROBE-AMS
	Route of administration ***(Mode of delivery)*** (e.g. Oral, ointment, etc.)	STROBE-AMS
	Rationale for ***grouping*** of antimicrobials (if applicable)	STROBE-AMS
	Who administered the antimicrobial treatment? (e.g. researcher, clinicians, nurses)	TIDieR
	Was the antimicrobial exposure planned to be ***personalised, or titrated***? (personalised doses by body weight, route specific administration, age, excipient)	TIDieR
	If so, was the what, why, when, and how of it described?	TIDieR
	Comparator fidelity – planned: How, and when antimicrobial consumption data were obtained (e.g. pharmacy record, patients' diary to be filled in daily, etc.)	TIDieR
Outcome measures	Defined pre-specified ***primary and secondary*** outcome measures	CONSORT
	When was each outcome measured?	CONSORT
	Definition of ***infection*** or ***colonisation*** used. If new definition, then evidence of robustness of the new definition	STROBE-AMS
	Definition of ***resistance*** (e.g. MIC values, cut-off points), multidrug resistance, and co-resistance used	STROBE-AMS

	Guidelines used in laboratory resistance measurements (NCCLS/CLSI, EUCAST, National German standards, etc.)	Added Item
Sampling: -	***site***	Added Item
	number of samples per person	Added Item
	sampling ***period***	Added Item
	method of sampling (e.g. midstream urine catch)	Added Item
	transport of samples (e.g. transport medium)	Added Item
Sample size	How was ***sample size*** determined?	STROBE/CONSORT
Measurement	Was resistance measured by an independent laboratory?	Added Item
	If not, were microbiologists blinded to exposure arm	Added Item
	Were ***microbiologists*** blinded to the ***time of sampling***?	Added Item
Analysis	***Unit of analysis*** defined (isolates, participants, other)	STROBE-AMS
	Statistical methods used to compare groups for primary and secondary outcomes	STROBE/CONSORT
	Methods for additional analyses, such as ***subgroup analyses*** (e.g., by class of antibiotic exposure) and ***adjusted analyses***	CONSORT/STROBE-AMS
Results		
Participants' characteristics and flow	Give ***characteristics*** of study participants (e.g., demographic, clinical, social)	STROBE/CONSORT
	Baseline resistance of the index pathogen	Added Item
	Time since ***last antibiotic exposure***	Added Item
	Description of ***potential confounders***	STROBE/STROBE-AMS
	Information on ***exposures*** (Day care centres for children, and long-term care facilities, nursing home and other healthcare settings for adults)	STROBE-AMS
	Indicate number of participants with ***missing data for each variable*** of interest	STROBE
	Summary of ***follow-up time*** (e.g., average and total amount)	STROBE
Numbers analysed (Exposure)	Incident ***total number*** of participants with/isolates of the ***index pathogen*** at nominated time points	Added Item
	Number of participants not carrying the index pathogen (i.e. ***sterile swabs***) at each time point	Added Item
	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***susceptible*** to the ***exposed antimicrobial or same class*** included in each analysis	Added Item
	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***resistant*** to the ***exposed antimicrobial or same class*** included in each analysis	Added Item
	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***susceptible*** to ***other antimicrobial or different class*** (Co-resistance data) included in each analysis	Added Item
	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***resistant*** to ***other antimicrobial or different class*** (Co-resistance data) included in each analysis	Added Item
	Incident number of participants with/isolates of ***other organisms*** at nominated time points ***susceptible*** to the ***exposed antimicrobial or same class*** (from other body sites e.g., bowel, nasopharynx, skin) included in each analysis	Added Item
	Incident number of participants with/isolates of ***other organisms*** at nominated time points ***resistant*** to the exposed antimicrobial or same class (from other body sites e.g., bowel, nasopharynx, skin) included in each analysis	Added Item
	Incident ***total number*** of participants with/isolates of ***other organisms*** at nominated time points (from other body sites e.g., bowel, nasopharynx, skin) included in each analysis	Added Item
	Number of ***adverse events*** occurred during antibiotic treatment reported (nausea, rash, diarrhoea, superinfections, etc.)	CONSORT
Numbers analysed (comparator) if applicable	Incident ***total number*** of participants with/isolates of the ***index pathogen*** at nominated time points	Added Item
	Number of participants not carrying the index pathogen (i.e. ***sterile swabs***) at each time point	Added Item
	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***susceptible*** to the ***exposed antimicrobial or same class*** included in each analysis	Added Item

	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***resistant*** to the ***exposed antimicrobial or same class*** included in each analysis	Added Item
	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***susceptible*** to ***other antimicrobial or different class*** (Co-resistance data) included in each analysis	Added Item
	Incident number of participants with/isolates of the ***index pathogen*** at nominated time points ***resistant*** to ***other antimicrobial or different class*** (Co-resistance data) included in each analysis	Added Item
	Incident number of participants with/isolates of ***other organisms*** at nominated time points ***susceptible*** to the ***exposed antimicrobial or same class*** (from other body sites e.g., bowel, nasopharynx, skin) included in each analysis	Added Item
	Incident number of participants with/isolates of ***other organisms*** at nominated time points ***resistant*** to the ***exposed antimicrobial or same class*** (from other body sites e.g., bowel, nasopharynx, skin) included in each analysis	Added Item
	Incident ***total number*** of participants with/isolates of ***other organisms*** at nominated time points (from other body sites e.g., bowel, nasopharynx, skin) included in each analysis	Added Item
	Number of ***adverse events*** occurred during antibiotic treatment reported (nausea, rash, diarrhoea, superinfections, etc.)	CONSORT
	Comparator fidelity/adherence – actual: The extent to which the antimicrobial was actually used or dispensed (if applicable)	TIDieR
Estimation	For each ***primary and secondary outcome***, and the estimated effect size and its precision (such as 95% confidence interval) (if applicable)	CONSORT
	Results of any ***other analysis*** performed, including ***subgroup analysis*** (by type of patients, type of microorganism, by class of antibiotic exposure)	STROBE/CONSORT/STROBE-AMS
Discussion		
	Limitations of the study, taking into account sources of potential bias or imprecision (both direction and magnitude of any potential bias)	STROBE/CONSORT
	Discuss study setting, type of hospital, local epidemiology for ***generalisability*** (external validity) of the study results	STROBE/CONSORT/STROBE-AMS
	Country's resistance pattern	Added Item
	If resistance-related outcomes are different between the comparison groups, discuss the implications for policy and practice	Added Item
	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence (if applicable)	CONSORT
Other information	Sources of ***funding*** and other support (such as supply of drugs), role of funders	STROBE/CONSORT

Supplementary Material 12. List of studies included in the systematic review and assessed for their quality. https://doi.org/10.6084/m9.figshare.7391876.v1

Trials

1. Berg HF, Tjhie JH, Scheffer GJ, Peeters MF, van Keulen PH, Kluytmans JA, Stobberingh EE: **Emergence and persistence of macrolide resistance in oropharyngeal flora and elimination of nasal carriage of Staphylococcus aureus after therapy with slow-release clarithromycin: a randomized, double-blind, placebo-controlled study**. *Antimicrob Agents Chemother* 2004, **48**(11):4183-4188.
2. Chern KC, Shrestha SK, Cevallos V, Dhami HL, Tiwari P, Chern L, Whitcher JP, Lietman TM: **Alterations in the conjunctival bacterial flora following a single dose of azithromycin in a trachoma endemic area**. *Br J Ophthalmol* 1999, **83**(12):1332-1335.
3. Cohen R, Bingen E, Varon E, de La Rocque F, Brahimi N, Levy C, Boucherat M, Langue J, Geslin P: **Change in nasopharyngeal carriage of Streptococcus pneumoniae resulting from antibiotic therapy for acute otitis media in children**. *Pediatr Infect Dis J* 1997, **16**(6):555-560.
4. Cohen R, Navel M, Grunberg J, Boucherat M, Geslin P, Derriennic M, Pichon F, Goehrs JM: **One dose ceftriaxone vs. ten days of amoxicillin/clavulanate therapy for acute otitis media: clinical efficacy and change in nasopharyngeal flora**. *Pediatr Infect Dis J* 1999, **18**(5):403-409.
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6. Dabernat H, Geslin P, Megraud F, Begue P, Boulesteix J, Dubreuil C, de La Roque F, Trinh A, Scheimberg A: **Effects of cefixime or co-amoxiclav treatment on nasopharyngeal carriage of Streptococcus pneumoniae and Haemophilus influenzae in children with acute otitis media**. *The Journal of antimicrobial chemotherapy* 1998, **41**(2):253-258.
7. Eliasson I, Holst E, Molstad S, Kamme C: **Emergence and persistence of beta-lactamase-producing bacteria in the upper respiratory tract in children treated with beta-lactam antibiotics**. *Am J Med* 1990, **88**(5A):51S-55S.
8. Gaynor BD, Chidambaram JD, Cevallos V, Miao Y, Miller K, Jha HC, Bhatta RC, Chaudhary JSP, Holm SO, Whitcher JP *et al*: **Topical ocular antibiotics induce bacterial resistance at extraocular sites**. *British Journal of Ophthalmology* 2005, **89**(9):1097-1099.
9. Ghaffar F, Friedland IR, Katz K, Muniz LS, Smith JL, Davis P, Reynolds J, McCracken GH, Jr.: **Increased carriage of resistant non-pneumococcal alpha-hemolytic streptococci after antibiotic therapy**. *J Pediatr* 1999, **135**(5):618-623.
10. Ghaffar F, Muniz LS, Katz K, Smith JL, Shouse T, Davis P, McCracken GH, Jr.: **Effects of large dosages of amoxicillin/clavulanate or azithromycin on nasopharyngeal carriage of Streptococcus pneumoniae, Haemophilus influenzae, nonpneumococcal alpha-hemolytic streptococci, and Staphylococcus aureus in children with acute otitis media**. *Clin Infect Dis* 2002, **34**(10):1301-1309.**[Same study reported in reference number 9]**
11. Huovinen P, Mattila T, Kiminki O, Pulkkinen L, Huovinen S, Koskela M, Sunila R, Toivanen P: **Emergence of trimethoprim resistance in fecal flora**. *Antimicrob Agents Chemother* 1985, **28**(2):354-356.
12. Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H: **Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study**. *Lancet* 2007, **369**(9560):482-490.

13. Malhotra-Kumar S, Van Heirstraeten L, Coenen S, Lammens C, Adriaenssens N, Kowalczyk A, Godycki-Cwirko M, Bielicka Z, Hupkova H, Lannering C *et al*: **Impact of amoxicillin therapy on resistance selection in patients with community-acquired lower respiratory tract infections: a randomized, placebo-controlled study**. *The Journal of antimicrobial chemotherapy* 2016, **71**(11):3258-3267.
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15. Nord CE, Peterson J, Ambruzs M, Fisher AC: **Levofloxacin versus azithromycin on the oropharyngeal carriage and selection of antibacterial- resistant streptococci in the microflora of healthy adults**. *Curr Med Res Opin* 2009, **25**(6):1461-1467.
16. Schrag SJ, Pena C, Fernandez J, Sanchez J, Gomez V, Perez E, Feris JM, Besser RE: **Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: a randomized trial**. *JAMA* 2001, **286**(1):49-56.
17. Skalet AH, Cevallos V, Ayele B, Gebre T, Zhou Z, Jorgensen JH, Zerihun M, Habte D, Assefa Y, Emerson PM *et al*: **Antibiotic selection pressure and macrolide resistance in nasopharyngeal Streptococcus pneumoniae: a cluster-randomized clinical trial**. *PLoS Med* 2010, **7**(12):e1000377.
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Prospective cohort studies

[1-8]

1. Brook I: **Emergence and persistence of beta-lactamase-producing bacteria in the oropharynx following penicillin treatment**. *Arch Otolaryngol Head Neck Surg* 1988, **114**(6):667-670.
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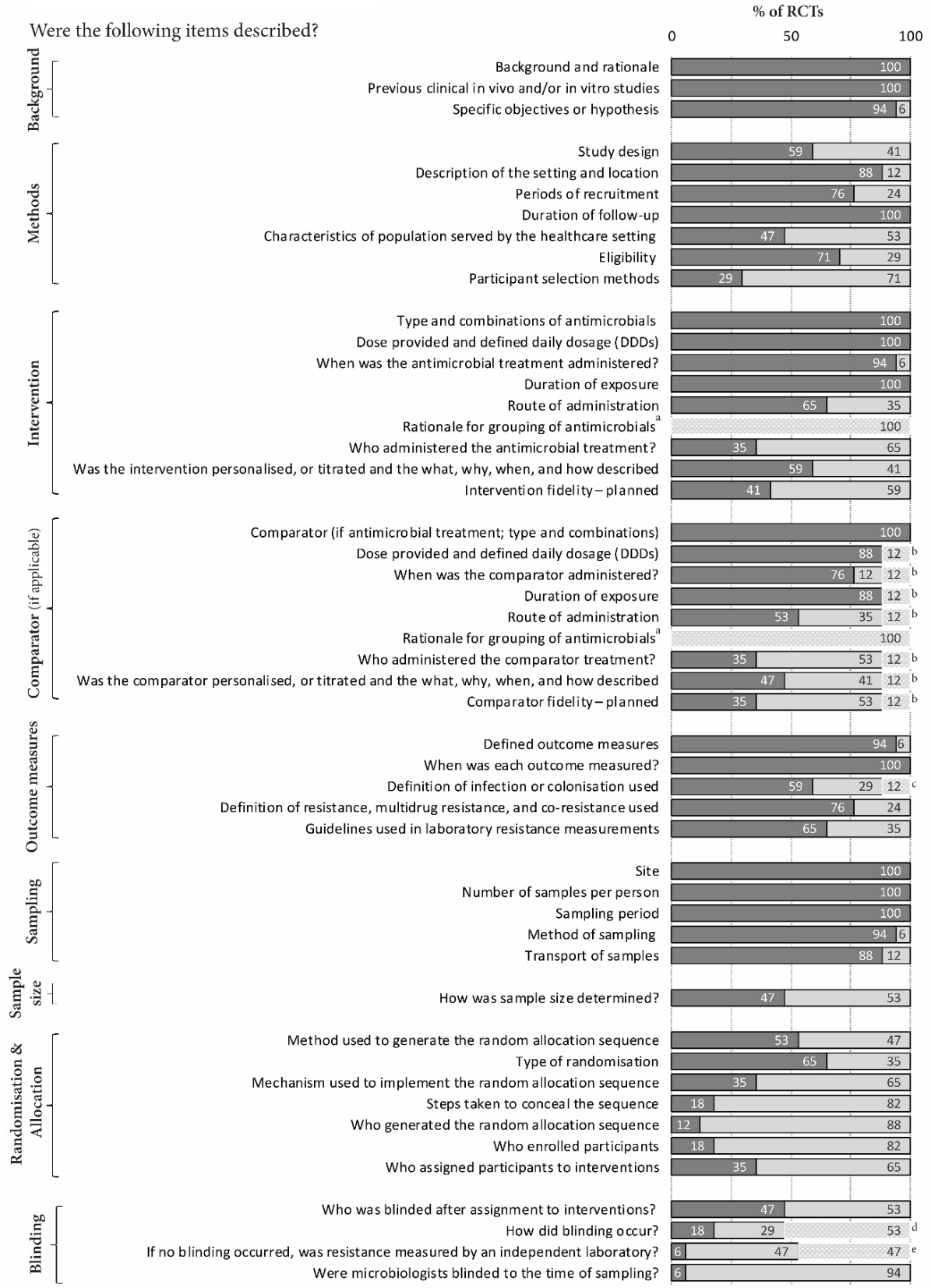
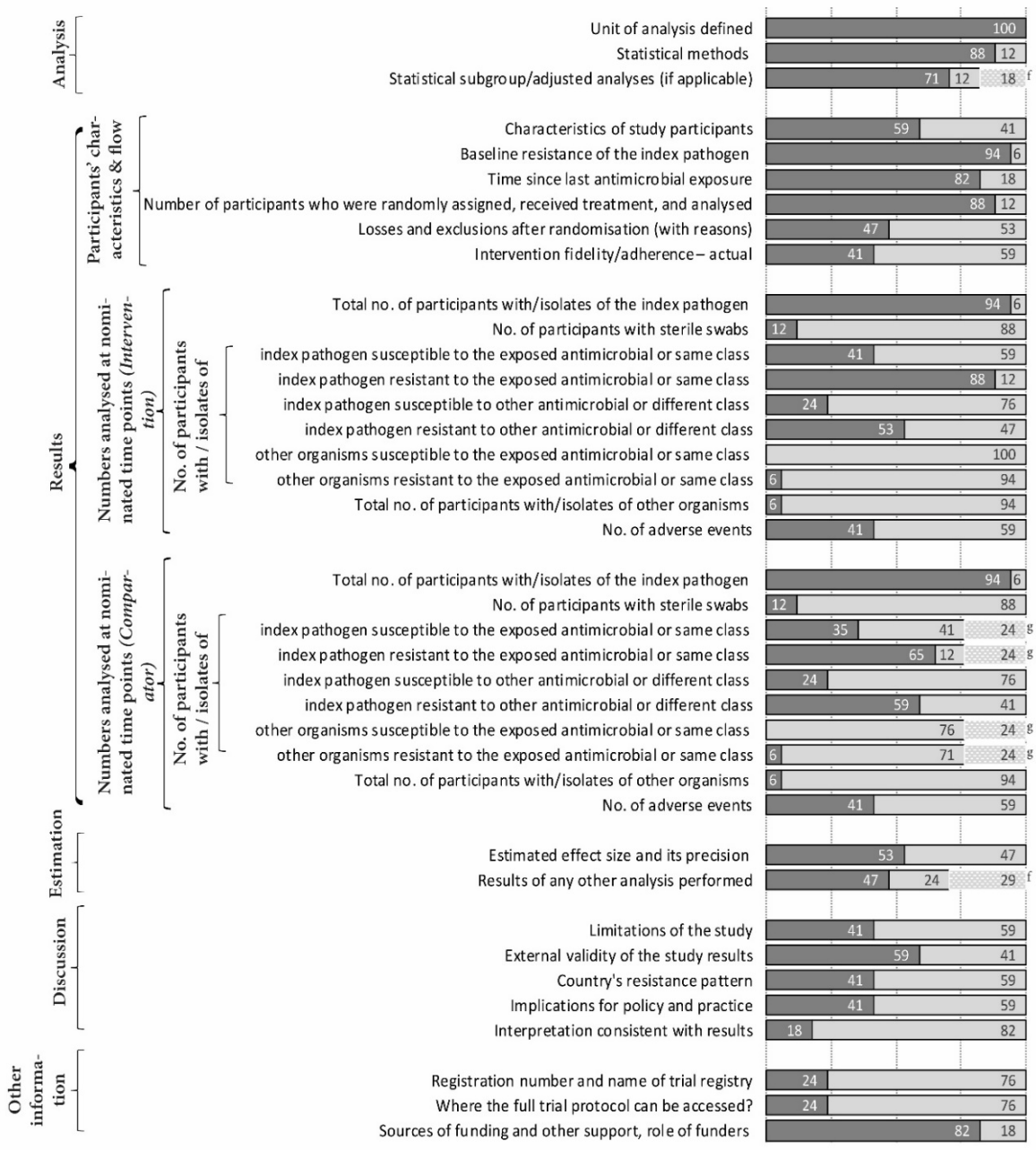
3. Conradi AD, Calbo E, Cuchi E, Puig RG, Garcia-Rey C, Boada LT, Diaz-Infantes M, Martin-Herrero JE, Garau J, Spanish Pneumococcal Infection Study N: **Impact of amoxicillin, associated or not with clavulanic acid, on pharyngeal colonization and selection of Streptococcus pneumoniae resistance in children under 5 years of age**. *Eur J Pediatr* 2007, **166**(5):467-471.
4. Dagan R, Leibovitz E, Greenberg D, Yagupsky P, Fliss DM, Leiberman A: **Dynamics of pneumococcal nasopharyngeal colonization during the first days of antibiotic treatment in pediatric patients**. *Pediatr Infect Dis J* 1998, **17**(10):880-885.
5. Lofmark S, Jernberg C, Jansson JK, Edlund C: **Clindamycin-induced enrichment and long-term persistence of resistant Bacteroides spp. and resistance genes**. *The Journal of antimicrobial chemotherapy* 2006, **58**(6):1160-1167.
6. Morita JY, Kahn E, Thompson T, Laclaire L, Beall B, Gherardi G, O'Brien KL, Schwartz B: **Impact of azithromycin on oropharyngeal carriage of group A Streptococcus and nasopharyngeal carriage of macrolide-resistant Streptococcus pneumoniae**. *Pediatr Infect Dis J* 2000, **19**(1):41-46.
7. Raum E, Lietzau S, von Baum H, Marre R, Brenner H: **Changes in Escherichia coli resistance patterns during and after antibiotic therapy: a longitudinal study among outpatients in Germany**. *Clinical Microbiology and Infection* 2008, **14**(1):41-48.
8. Varon E, Levy C, De La Rocque F, Boucherat M, Deforche D, Podglajen I, Navel M, Cohen R: **Impact of antimicrobial therapy on nasopharyngeal carriage of Streptococcus pneumoniae, Haemophilus influenzae, and Branhamella catarrhalis in children with respiratory tract infections**. *Clin Infect Dis* 2000, **31**(2):477-481.

Supplementary Material 13. Quality of reporting, % of RCTs meeting each item (studies= 17, including if applicable items)

https://doi.org/10.6084/m9.figshare.7391891.v1

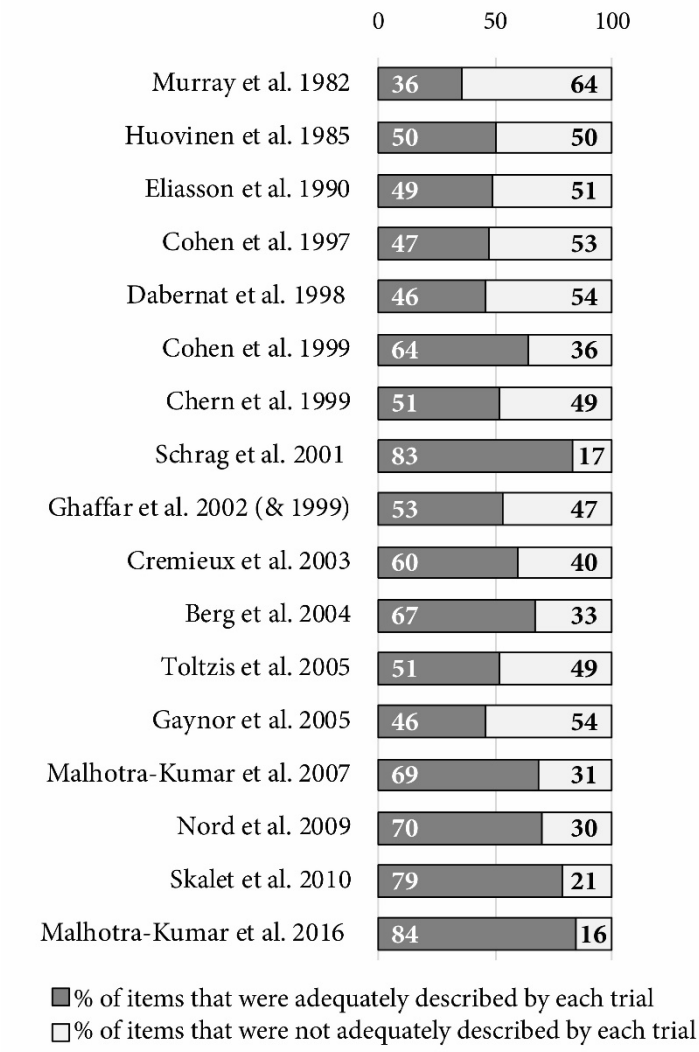




[a] Not applicable because it was not within the scope of the main review
[b] Not applicable for studies that compared the intervention to a no-exposure (control) group
[c] Not applicable for studies that recruited healthy participants
[d] Only applicable for blinded studies
[e] Only applicable for studies where no blinding occured
[f] Only applicable for studies that reported subgroup/adjusted analyses
[g] Not applicable for studies that compared the intervention to a control/placebo group

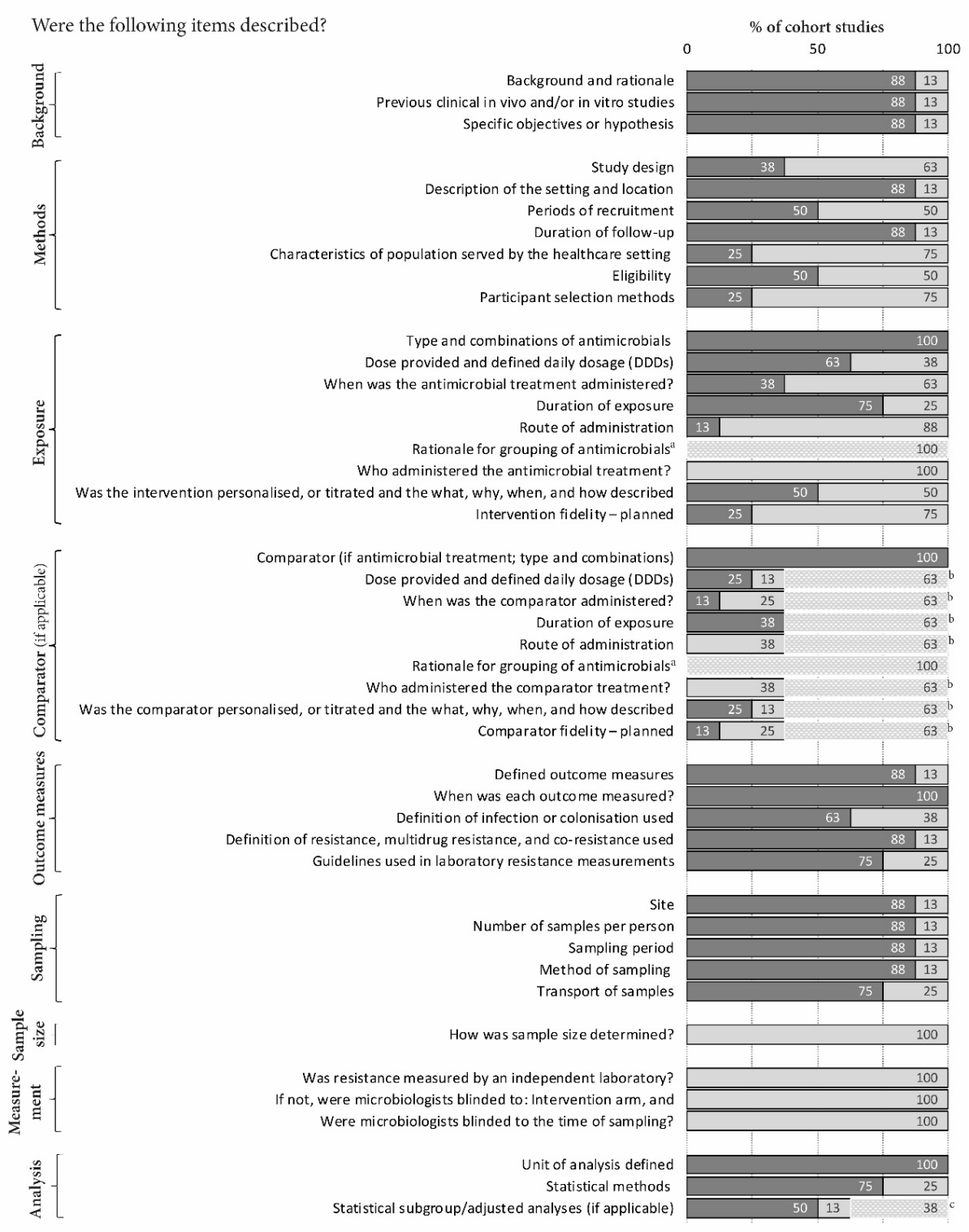
Supplementary Material 14. Quality of reporting, % of items described by each trial (studies= 17, mandatory items= 70)

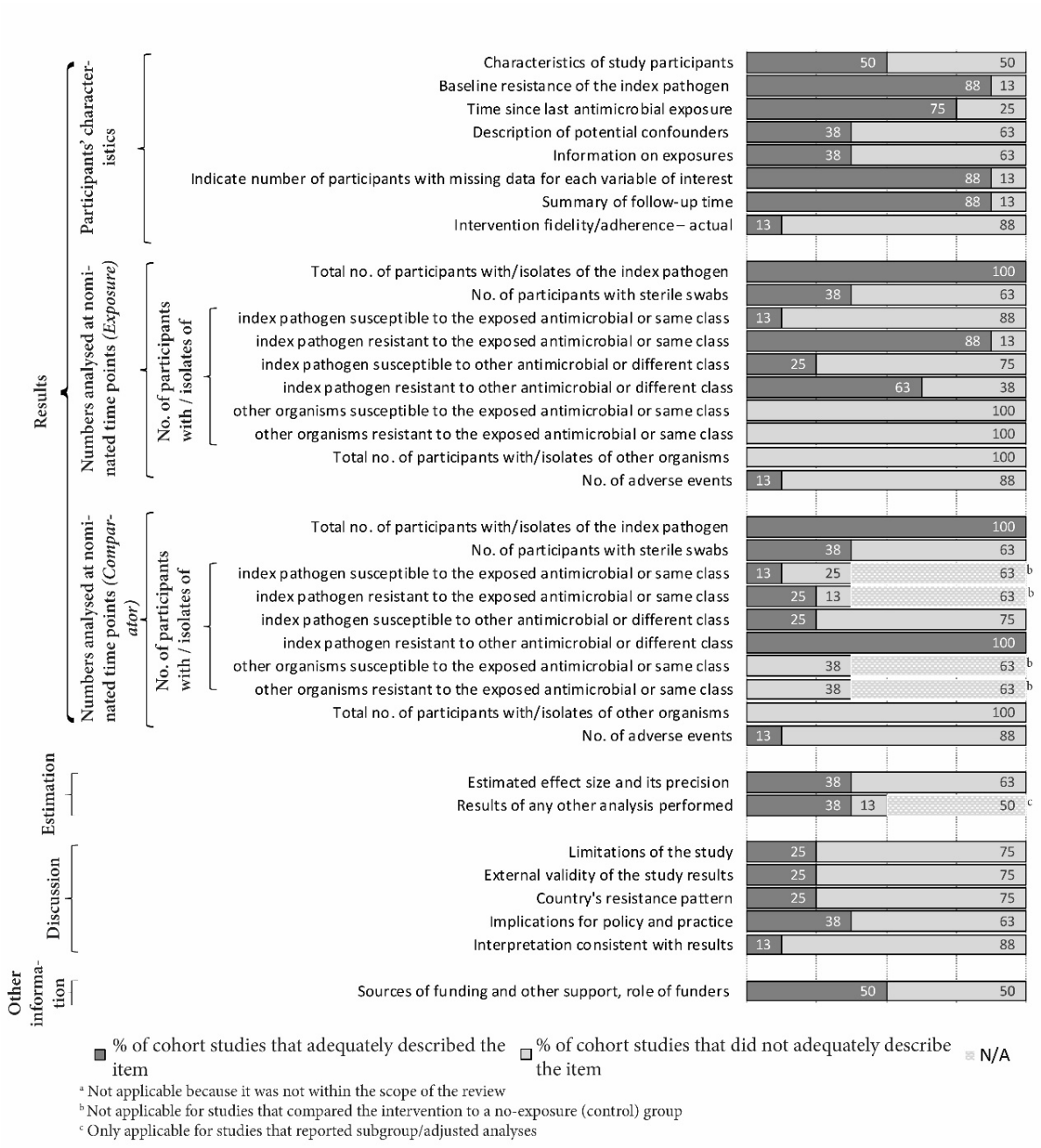
https://doi.org/10.6084/m9.figshare.7391906.v1



Supplementary Material 15. Quality of reporting, % of cohort studies meeting each item (studies= 8, including if applicable items)

https://doi.org/10.6084/m9.figshare.7391918.v1

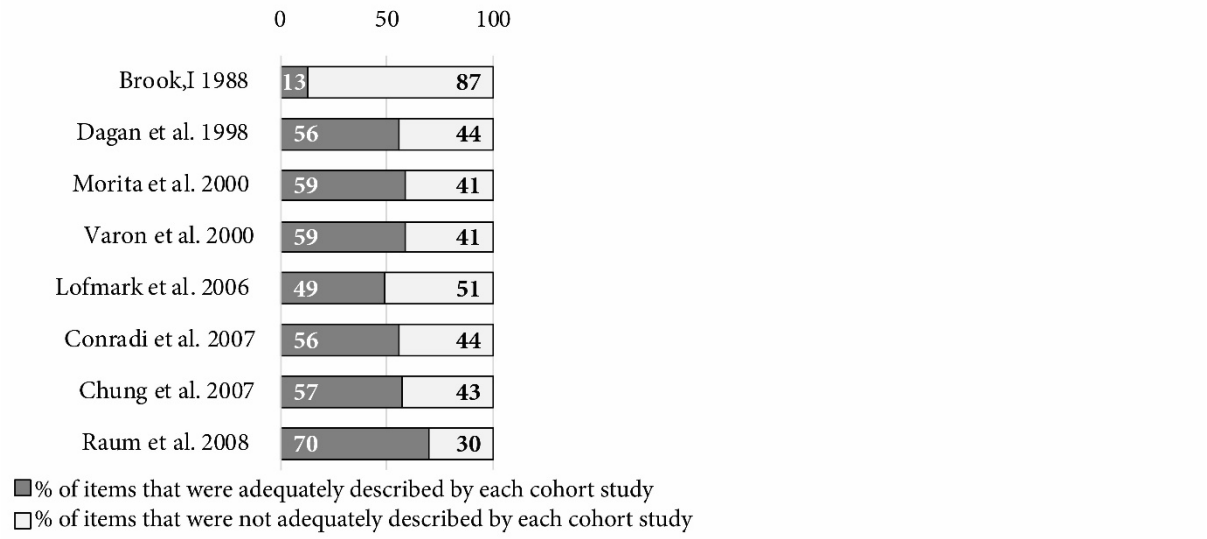




[a] Not applicable because it was not within the scope of the review
[b] Not applicable for studies that compared the intervention to a no-exposure (control) group
[c] Only applicable for studies that reported subgroup/adjusted analyses

Supplementary Material 16. Quality of reporting, % of items described by each cohort study (studies= 8, mandatory items= 63)

https://doi.org/10.6084/m9.figshare.7391927.v1



Chapter 7

General Discussion

Preamble

This chapter draws together the findings and novel contributions of all four research studies within the broader scope of the aims of the whole thesis. It also discusses the implications of these findings for clinical practice, policy makers and future research.

The key aims of this thesis were to explore: 1) patient-clinician communication of antibiotic benefits and harms, including antibiotic resistance, during ARI consultations; 2) patients' understanding of antibiotic resistance, and aspects of it, such as resistance decay and spread among those who live in close proximity; and how these influenced patients' attitudes towards antibiotic use; and 3) to update the current evidence about resistance development and decay. The four studies presented in this thesis (Chapters 3-6) explored these key objectives through the focused research questions presented in Chapter 1. The thesis makes an original contribution to the evidence behind resistance decay and furthers understanding of the elements of the communication of antibiotic benefits and harms (including antibiotic resistance) within GP consultations with patients with ARIs. By drawing together these research findings, this chapter identifies implications for clinical practice, the conduct of resistance research, and provides some recommendations for policy.

Overview of the problem

As outlined in Chapter 2, antibiotic resistance is a growing global public health crisis (1). Antibiotic resistance emerges as a direct result of individual antibiotic use (2-4), human-human transmission from other family and household members (5), or through interaction with the environment (6-8). Antibiotic resistance increases patients' morbidity and mortality (9), healthcare resource utilisation (10, 11), and has an enormous economic impact (12).

Antibiotics are overused and abused, particularly in primary care (13). In Australia, over 30 million antibiotic prescriptions were dispensed in 2015 (14, 15). More than 60% of patients consulting in primary care with an ARI received an antibiotic, despite evidence from systematic reviews that antibiotics have marginal benefits for most ARIs (16-23). Causes for this overuse include both clinician and patient-related factors, such as indifference to learning more about reducing antibiotic prescribing in ARI management (24), diagnostic uncertainty (25-27), patients' perceived demand of antibiotics (26, 28, 29), and consultation time pressure (30).

Several strategies targeting the previously mentioned factors have been promoted to reduce antibiotic use (31). One of these is better communication,

such as through shared decision making (SDM) (32). Consultations for ARIs are especially suitable for SDM because of the delicate balance between antibiotic benefits and harms, and people's misperceptions of the need for and benefits of antibiotics (33). Antibiotic resistance is an unusual harm as it does not affect individuals during their current illness, but may affect the course of treatments for their future illnesses of the same (or other) infection. Moreover, individuals may spread resistance strains to those who live in close proximity (such as family members) and the wider community.

Summary of thesis findings

Patient-clinician communication of antibiotic treatment for ARIs

Study 1 (Chapter 3) examined the extent of shared decision making in ARI consultations, including if and how clinicians communicated about antibiotic benefits and harms. In addition, the study explored whether specifically developed decision aids for common ARIs (sore throat, acute bronchitis and acute otitis media) were used when available and if they supported clinicians in facilitating shared decision making and having a balanced discussion about antibiotic benefits and harms with their patients.

This study found that during routine clinical consultations with ARI patients, clinicians generally poorly communicate antibiotic benefits and harms, with little mention or explanation about antibiotic resistance as a possible risk. Clinicians discussed antibiotic benefits and harms more frequently and more comprehensively, and included antibiotic resistance as one of the potential harms of using antibiotics, when decision aids were used.

Information provision by clinicians is necessary to enable patients to make an informed decision. Part of this includes having a balanced benefit-harm discussion with their patients. Study 1 suggests that using decision aids can help facilitate SDM within consultations, improving communication about antibiotic benefits and harms, including antibiotic resistance in the discussion of antibiotic harms.

Patients' understanding of aspects of antibiotic resistance and its influence on attitudes to antibiotic use

Study 2 (Chapter 4) was a qualitative analysis conducted in a sub-sample of patients with ARIs recruited in Study 1. It explored patients' understanding of antibiotic resistance, aspects of resistance such as resistance decay and spread, and patients' attitudes towards antibiotic use. This study is original as no previous research has examined patients' understanding of antibiotic resistance decay or spread or influence of this knowledge on attitude about antibiotic use.

As outlined in Chapter 4, five major themes emerged from the thematic analysis of the qualitative interviews. The analysis showed that participants' understanding of many aspects of antibiotic resistance was limited. Although participants generally understood the link between antibiotic use and developing antibiotic resistance, they were confused about the nature of antibiotic resistance: most believed that resistance does not affect the individual. Most participants were not aware that resistance can decay over time, and among those who were, the estimate of the time to decay were wide (from days to decades). Awareness that resistance could be transmitted among family members was low. After an explanation from the interviewer about resistance decay and its transmission between people who live in close proximity, some participants indicated that knowing this would alter their future use of antibiotics by not taking them for minor infections. Another finding is that patients with personal experience of antibiotic resistance were the most reluctant to use them again; such participants felt strongly about reserving their use for serious illness or only when needed.

Evidence about resistance development and decay

Previous research had reported that antibiotic resistance takes up to 12 months to decay from the maximum directly after antibiotic exposure (4). However, the updated and methodologically more rigorous review in Study 3 (Chapter 5) showed that antibiotic resistance decays faster than this. Antibiotic resistance increased immediately after antibiotic exposure with different odds of isolating resistance strains differing by the type of antibiotic exposure and bacterium (Fig. 7 to 9). Although Study 3 showed that resistance decays with time, the paucity of studies investigating this meant only specific bacteria such as *S. pneumonia* and

H. influenzae and exposure to specific antibiotic classes, such as penicillins and cephalosporins could be reported. The original contribution of this review is that it is the most comprehensive systematic review, which focused solely on studies with prospective designs reporting antibiotic resistance after exposure to antibiotics in primary care.

The review highlighted two main issues about the existing research: 1) paucity of evidence investigating resistance decay; and 2) incomplete reporting of antibiotic resistance in the included studies. Thus, further exploration of the quality of reporting against the currently available reporting guidelines was conducted in Study 4 (Chapter 6).

Reporting quality of antibiotic resistance studies

Study 4 identified deficiencies in the description of aspects of the methods such as blinding and sample size determination. Moreover, crucial details about antibiotic resistance reporting, such as the incident numbers of patients or isolates analysed at each bacterial isolation time point were among the most poorly reported items. Incomplete reporting of trials and cohort studies hinders the interpretation and use of results in clinical practice, further research, and meta-analysis.

Strengths and limitations of the thesis

Each study in this thesis has strengths and limitations which have already been discussed in the preceding chapters. A summary of these is listed below in Table 6.

Table 6. Strengths and limitations of individual studies in the thesis

	Strengths	Limitations
Study 1 (Observational study, Chapter 3)	▪ Minimised bias as clinicians did not choose which consultations to record. ▪ Two independent raters scored the consultations.	▪ Not a true randomised trial. ▪ A small number of consultations. ▪ GPs self-selected to participate in the study. ▪ Presence of an audio recorder during the consultation and the researcher in the waiting room (possible Hawthorne effect). ▪ Possibly un-representative sample.
Study 2 (Qualitative study, Chapter 4)	▪ The first study to explore patients' knowledge about the potential for antibiotic resistant organisms to spread between people in close proximity and that antibiotic resistance decays over time. ▪ Thematic analysis was done by two researchers independently.	▪ The risk that the knowledge of antibiotic resistance was influenced by GPs' use of a patient decision aid for a small number of participants. ▪ Participants did not have the opportunity to provide feedback on the themes derived from the interviews.
Study 3 (Systematic review and meta-analysis, Chapter 5)	▪ Systematic and transparent search strategy. ▪ Studies with retrospective designs posing a high risk of bias were excluded. ▪ Reporting of time to decay periods after antibiotic exposure were aligned across the different bacteria and antibiotic classes to enable better comparisons.	▪ Extraction of unadjusted status of the odds ratios from the included studies vs study authors' altered some estimates. ▪ Multiple confounders other than antibiotic exposure might affect the development of resistance within individuals and the review could not examine this. ▪ Poor reporting of how resistance data were analysed.

		▪ Some authors did not respond to requests to clarify aspects of their methods and data.
Study 4 (Quality of reporting study, Chapter 6)	▪ The first study to examine the quality of reporting of prospective studies which have measured antibiotic resistance. ▪ Two researchers independently performed the data extraction.	▪ Included studies are limited to those included in Study 3 ▪ Modified checklists were not formally assessed.

The broad and inclusive nature of data collection processes (e.g. two independent reviewers/raters/coders for each study, rigorous systematic searching, and for participant recruitment) are common strengths across the studies. Consequently, this thesis has the key strength of providing a broad picture of the current state of evidence for antibiotic resistance decay, patient-clinician communication about antibiotic benefits and harms, and patients' understanding of and attitude towards aspects of antibiotic resistance for ARIs. Additionally, the use of rigorous study methodologies and standardised reporting guidelines and risk of bias tools (COREQ checklist, PRISMA statement, Cochrane Risk of Bias tool, ROBINS-I tool, STROBE statement and its extension STROBE-AMS, TIDieR checklist, and CONSORT statement) assists this thesis to make a valuable contribution to the current body of evidence.

The main limitation in the implications for the findings of this thesis derives largely from the restricted number of participants and study sites in the primary research studies, which risks the generalisability of the study results.

Implications and recommendations of findings for clinical practice and policy

Antibiotic resistance presents a threat to public health, the safety and efficacy of health interventions and can lead to increased morbidity and mortality and healthcare-associated expenses (9, 12). National strategies tackling antibiotic resistance through antibiotic stewardship programs are an important part of the

approach to preserving the effectiveness of antibiotics (34). From the findings of this thesis, these implications and recommendations for clinical practice and policy have been derived:

Recommendation 1: *Efforts to promote SDM within consultations for ARIs in primary care should be continued, particularly by using decision aids.*

Several interventions which aim to facilitate SDM have been shown to be effective in reducing antibiotic prescribing in primary care (32). However, in the Australian general practice context, brief decision aids may be the most likely to be implemented, as existing interventions are difficult to adopt (costly and more time consuming) (35). Thus as part of addressing the crisis of antibiotic resistance, it is worth exploring further different ways to facilitate SDM. This thesis (Study 1, Chapter 3) provides support for the growing movement towards implementation of SDM within consultations for ARIs as it found that utilising a decision aid facilitated elements of SDM and more comprehensive communication about antibiotic benefits and harms. An important caveat to note while interpreting the study findings is that although the practices were participating in a randomised trial, this substudy was not a randomised trial. However, the logistics of measuring SDM in every consultation in a randomised trial made this not feasible. It is prohibitively expensive to screen and gain consent from every patient who visits each GP in every practice for the duration of the main trial.

With or without these specific decision aids, clinicians should aim to have consultations with their patients that help them to reach an informed and collaborative decision about the use of antibiotics for ARIs.

Recommendation 2: *Public health messages could incorporate messages that target patients' misunderstandings about: what antibiotic resistance is; individual contribution to its development; individual implications; its spread between family members; and perhaps its decay with time.*

Study 2 revealed that people attending their GP had poor knowledge about antibiotic resistance, specifically its spread among people who live in close proximity, and that antibiotic resistance decays with time from the maximum directly after antibiotic exposure. In some participants, knowing that resistance decays over time if antibiotics are not used, provided hope for conserving antibiotics, and for others, learning that antibiotic resistance can be transmitted

among people who live in close proximity such as family members, was a reason not to use them. When considered together, the findings from Studies 2 and 3 highlight the potential to further research and consider providing information that: 1) resistance that will occur after exposure to even a single antibiotic course and that antibiotics might not work until decay occurs (if serious illness develops); and 2) resistance could be transmitted between people who live in close proximity to the patient before prescribing antibiotics for minor infections such as ARIs. However, the optimal information about antibiotic use and resistance to include in public health messages, and clinical consultations, needs further testing (see implications for future research).

Recommendation 3: *That antibiotic resistance decays at different rates for different antibiotic classes and bacteria than previously reported, should be considered by clinicians when choosing which (if any) antibiotics for their patients.*

Since 2010, the message about antibiotic resistance has been that it takes up to 12 months to decay in community-based individuals following antibiotic exposure (4). However, Study 3 showed this might not be true for all bacteria or following exposure to the different antibiotic classes. The review found that it takes up to one month for resistant strains of S. pneumonia bacteria to decay after individual exposure to penicillin- or cephalosporin-class antibiotics. The paucity of evidence limited exploration of the decay behaviour following exposure to other classes. However, the limited evidence in studies which reported resistance after exposure to macrolides showed that it might take up to 6 months for resistant strains of S. pneumonia to decay. If clinicians were aware of and considered this information and prescribed antibiotic classes associated with quicker decay, this may reduce the emergence of resistance within the community. This information is important for policy makers and government advisory boards (such as The Department of Health and NPS MedicineWise). These organisations could use these findings in coordinated strategies and interventions to promote the use of antibiotics associated with quicker decay.

Recommendation 4: *Trials investigating the clinical efficacy of any antibiotic interventions should report antibiotic resistance as a key harm of antibiotics.*

Although many studies are published every year investigating the clinical efficacy of different antibiotic classes in the treatment of different infections, few report

antibiotic resistance as a direct harm from using antibiotics. Even if when it is reported, as the findings from Study 4 show, it is not reported optimally.

Implications of findings for future research

Following the research conducted for this thesis, several unanswered questions have emerged. These are briefly outlined below and should be addressed in future research:

1. *Does knowledge about resistance decay influences GPs' attitude towards antibiotic prescribing for ARIs?*

   In Chapter 4, patients' understanding of antibiotic resistance and its aspects was examined. However, examining clinicians' knowledge about resistance decay might influence their attitudes towards antibiotic prescribing. As described in Chapter 2, many clinicians believe that they do not contribute to the problem of antibiotic resistance and that it is a hospital-based problem rather than a community problem (36). Other qualitative research has suggested that linking clinicians' prescribing with local resistance rates may motivate clinicians to change their prescribing behaviour (37, 38). It has been suggested that future research interventions that aim to reduce antibiotic prescribing should target clinicians' perception of antibiotic benefits to their patients, which is outweighed by the individual and societal harms of antibiotic resistance (38).

   Providing clinicians with information about resistance development after antibiotic use in community individuals, might, or might not, change their prescribing behaviour. The results from the systematic review and meta-analysis (Chapter 5) showed that time to resistance decay is faster than previously reported (2). It is unknown if this knowledge would mitigate or add to the problem of inappropriate antibiotic prescribing. Future research could shed light on how this might influence antibiotic prescribing.

2. *How does personal experience of antibiotic resistance influence attitudes towards the antibiotic use of individual patients?*

The findings of Study 2 (Chapter 4) suggested that patients who had personal experience with antibiotic resistance were the most reluctant to use them again, instead preferring to reserve their use for serious illnesses. This area has not been sufficiently examined. It might assist in developing public health messages or information that can be used in consultations. In a survey among the general population in Germany, people who knew someone suffering from multi-drug resistant organisms demanded more information on antibiotic resistance from their GP and fewer antibiotics compared to those who did not know someone with antibiotic resistance (39).

3. *What optimal information about antibiotic use and resistance should be included in public health messages?*

   This future research area arises from Study 2 and the literature review in Chapter 2. In a review of the characteristics and outcomes of large-scale public health campaigns aimed at improving the use of antibiotics (40), campaigns promoted key messages that antibiotic resistance is a problem and that viruses cause most respiratory infections. However, campaigns did not convey information about antibiotic harms, and it was not clear which campaign elements were the reason behind the change of behaviour that led to a reduction in antibiotic use (40). It is also unknown if a greater reduction in antibiotic use could be achieved if different or additional elements and messages were incorporated into campaigns. Study 2 showed that information about aspects of antibiotic resistance (such as resistance decay and spread) might contribute to altering people's attitude towards antibiotic use, at least for minor infections. There is a need to identify areas with a paradoxical effect on the public's attitude towards antibiotic use, ensuring optimal information about antibiotic use and resistance can be included in public health messages.

4. *How to improve the reporting quality of antibiotic resistance research?*

   This issue arises from Studies 3 and 4 (Chapter 5 and 6). Many of the studies that reported resistance after community antibiotic exposure did not report key details. For example, most studies did not report the incident numbers of resistant and susceptible isolates analysed at each time-point,

and blinding was inadequately reported in just over half of the trials and all prospective cohort studies.

Although guidelines are available for optimising reporting of epidemiological studies in Antimicrobial Stewardship (STROBE-AMS) (41), they are not designed for use with prospective design studies. Moreover, there are concerns about the generalisability of STROBE-AMS. The authors describe limiting their literature review to only articles which analysed the association between antibiotic exposure and the acquisition of Methicillin-resistant Staphylococcus aureus (MRSA) and/or multidrug-resistant Acinetobacter baumannii.

Collecting and aggregating expert opinion using recommended methods (42) to develop a better and globally endorsed reporting checklist maybe worthwhile. The existence of a reporting guideline and checklist is not sufficient on its own to improve reporting quality. However, endorsement of guideline use and adequate reporting of antibiotic resistance studies is needed by researchers, peer-reviewers, and journal editors of relevant journals.

5. *Is time to resistance decay different after exposure to different antibiotic classes?*

   Study 3 showed that the behaviour of resistance decay varies according to the class of antibiotic exposure and type of bacterium. However, the paucity of available data limited the investigation of resistance decay among other classes and bacteria beyond what was described in Study 3. Many studies investigating resistance reversibility are laboratory-bench-top, examining the 'fitness costs' for bacteria required for antibiotic reversibility to occur (43). However, more RCTs are required to empirically test the decay of antibiotic resistance in patients, because of the complexity of bacteria population dynamics. These would enable the enhancement of antibiotic therapeutic guidelines to accommodate the potential of different antibiotic resistance generation among different antibiotic-infection dyads. Consequently, as previously described, guiding future antimicrobial stewardship programs to promote the use of antibiotics associated with quicker decay.

Conclusion

This thesis highlighted the need for enhanced communication between clinicians and patients with ARIs about antibiotic use, including a balanced conversation about antibiotic benefits and harms, including discussion about how resistance is a potential harm of antibiotics. This thesis also suggested potential methods of improving this communication such as patient decision aids, possible public health messages, and information about resistance development and decay that may assist clinicians' prescribing decisions. Simultaneous efforts to tackle antibiotic resistance from improving its communication in clinical consultations, more nuanced public health messages, to its better reporting in medical journals, need to be implemented to reduce its global burden and personal and societal consequences.

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Appendices

Appendix 1. GP consent form and information sheet

GP Consent Form (consultation recordings)
RO-15543

Effect of decision aids for acute respiratory infections on the use of antibiotics in general practice: a cluster randomised controlled trial
Investigators: Professor Tammy Hoffmann, Professor Chris Del Mar, Dr Mina Bakhit

Declaration by participant

I have read the Participant Information Sheet.

I understand the purpose, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to take part in this research project as described and understand that I am free to withdraw at any time during the project without any negative consequences to me or my practice.

I understand that I will receive a copy of the participant information sheet and this form.

☐ Please tick here if you wish to be given a summary of the results of the study once it has been completed.

Please provide the email address you would like this to be sent to:

Name of Participant (Please print) _____

Signature of Participant _____ Date _____

Declaration by Researcher[†]

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Researcher[†] (please print) _____

Signature or researcher _____ Date _____

[†] An appropriately qualified member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

General Practitioner Information Sheet (audiorecording of a sample of consultations)

BOND UNIVERSITY
FACULTY OF HEALTH SCIENCES & MEDICINE

Full project title: Effect of decision aids for acute respiratory infections on the use of antibiotics in general practice: a cluster randomised controlled trial

Investigators: Professor Tammy Hoffmann, Professor Chris Del Mar, Dr Mina Bakhit

You are invited to participate in this study because you have consented to take part in the randomised trial of decision aids about antibiotic use in acute respiratory infections. This information sheet explains a sub-study that we are conducting at the same time as the trial

Your involvement in this substudy will be the same, regardless of whether your practice is randomised to the intervention or control groups of the trial.

What is the aim of this study?

This study aims to examine the conversation that occurs between GPs and patients with acute respiratory infections and how the decision-making about antibiotic use occurs. In GPs who are randomised to the intervention group, we will also examine how decision aids are integrated into consultations.

What does participation in this study involve?

- At **each practice**, we would like to **audio record 10 consultations** between consenting GPs and consenting patients who have sore throat, acute otitis media, or acute bronchitis.

- For a few days of the trial, until 10 consultations have been recorded, a researcher will be located in the waiting room of your practice. The researcher will have a handheld audio recording device and patient information sheets and consent forms. The method of recruiting patients will vary according to each practice's preference and workflow, with the options of:
    - patients or parents of children who present with one of the target infections will be invited to participate by their GP at the beginning of the consultation, have the study explained to them, written consent obtained, and the GP will record the consultation;
    - during these few days, displaying a sign in the reception area advising that patients presenting with sore throat, cough, or ear infection are invited to participate in a research study. When patients indicate interest in participating, the researcher who is present in the practice's waiting room will be able to explain the study to them, invite consent, and provide patients with the audiorecorder to take into the consultation with them.
- After the consultation, the researcher will talk with the patients for a few minutes and ask them a few questions about antibiotics and their confidence in making decision about antibiotic use.

What are the possible benefits of participating in this study?

There may not be any individual benefit to you from participating.

What are the possible risks of participating in this study?

Participating in this study is unlikely to have any risks to your physical or psychological wellbeing.

Do I have to take part in this study?

Participation in this sub-study is **completely voluntary**. Choosing to participate in it will have no impact on your future relation with Bond University or the health system. If you decide to participate, you can withdraw your consent and discontinue participation at any time without prejudice. You can withdraw your consent from participating in this sub-study and remain involved in the main trial.

What will happen to information about me?

Data collected in this study will be treated with complete confidentiality and not made accessible to any person outside of the research team. Data published or presented from the study will not include any information that can identify you or your practice. Data will be kept secure, password protected and stored in a secure location at Bond University for a period of 5 years in accordance with the guidelines set out by the Bond University Human Research Ethics Committee.

Will I receive the results of this study?

If you would like to receive a copy of the results of this sub-study please tick that box on the consent form.

Who has approved this study?

This study has been reviewed and approved by Bond University Human Research Ethics Committee. This study adheres to the Guidelines of the ethical review process of Bond University and the National Statement on Ethical Conduct in Human Research.

Who can I contact if I have questions?

If you have any questions about the study, please contact the researcher who provided you with this sheet or any of the investigators listed below:

Dr. Mina Bakhit	0499 461 022	mbakhit@bond.edu.au
Amanda Murray (Trial co-ordinator)	0474 013 381	cremara@bond.edu.au
Professor Tammy Hoffmann	5595 2504	thoffmann@bond.edu.au
Professor Chris Del Mar	5595 5522	cdelmar@bond.edu.au

Should you have any complaints concerning the manner in which this research is being conducted please contact:

Senior Research Ethics Officer

Bond University Human Research Ethics Committee,

C/o Bond University Office of Research Services

Thank you for taking time to read about this research study.
Yours sincerely,
Dr Mina Bakhit, Professor Tammy Hoffmann, Professor Chris Del Mar
Centre for Research in Evidence-Based Practice
Faculty of Health Sciences and Medicine
Bond University

Appendix 2. Patient/parent consent form and information sheet

Patient/Parent Consent Form
RO-15543

Effect of decision aids for acute respiratory infections on the use of antibiotics in general practice: a cluster randomised controlled trial

Investigators: Dr Mina Bakhit, Professor Tammy Hoffmann, Professor Chris Del Mar

Declaration by participant

I have read the Participant Information Sheet.

I understand the purpose, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to take part in this research project as described and understand that I am free to withdraw at any time during the project without any negative consequences to me or my child.

I understand that I will receive a copy of the participant information sheet and this form.

☐ Please tick here if you wish to be given a summary of the results of the study once it has been completed.

Please provide the email address you would like this to be sent to:

Name of Participant (Please print) _____

Signature of Participant _____ Date _____

Declaration by Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Researcher† (please print) _____

Signature or researcher _____ Date _____

† An appropriately qualified member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Patient/Parent Information Sheet

Full project title: Effect of decision aids for acute respiratory infections on the use of antibiotics in general practice: a cluster randomised controlled trial

Investigators: Dr Mina Bakhit, Professor Tammy Hoffmann, Professor Chris Del Mar

You are invited to participate in a research study.

What is the purpose of this study?

- This study will examine the conversation that occurs between GPs and patients with acute respiratory infections (sore throat, ear infection, or cough) and how the decision-making about antibiotic use occurs.
- We also wish to explore patients' confidence in making decisions about antibiotic use and their understanding of antibiotic resistance.

What does participation in this study involve?

- If you or your child has a sore throat, middle ear infection, or an acute cough (bronchitis), we would like to audiorecord the consultation between yourself and the GP that you see. The GP also has to provide consent for this to happen.

- After you have seen the GP, one of the research team will talk with you briefly and ask you a few questions about antibiotics and your confidence in making decision about antibiotic use. This will take about 5 minutes.

What are the possible benefits of participating in this study?

There may not be any individual benefit to you from participating. However, your participation will benefit the broader community by increasing understanding of decision making about antibiotics for acute respiratory infections and how to help patients make informed decisions about this.

What are the possible risks of participating in this study?

Participating in this study is unlikely to have any risks to your physical or psychological wellbeing.

Do I have to take part in this study?

Participation in this study is **completely voluntary**. Choosing to participate in it will have no impact on your future relation with Bond University, your GP, or the general practice. If you decide to participate, you can withdraw your consent and discontinue participation at any time without prejudice. You can withdraw your consent from participating at any time.

What will happen to information about me?

Data collected in this study will be treated with complete confidentiality and not made accessible to any person outside of the research team. Data published or presented from the study will not include any information that can identify you or your child. Data will be kept secure, password protected and stored in a secure location at Bond University for a period of 5 years in accordance with the guidelines set out by the Bond University Human Research Ethics Committee.

Will I receive the results of this study?

If you would like to receive a copy of the results of this study, please tick that box on the consent form.

Who has approved this study?

This study has been reviewed and approved by Bond University Human Research Ethics Committee. This study adheres to the Guidelines of the ethical review process of Bond University and the National Statement on Ethical Conduct in Human Research.

Who can I contact if I have questions?

If you have any questions about the study, please contact the researcher (Dr Mina Bakhit) who provided you with this sheet or any of the investigators listed below:

Dr Mina Bakhit	Tel: (07) 5595 5201	email: mbakhit@bond.edu.au
Professor Tammy Hoffmann	Tel: (07) 5595 2504	email: thoffmann@bond.edu.au
Professor Chris Del Mar	Tel: (07) 5595 5522	email: cdelmar@bond.edu.au

Should you have any complaints concerning the manner in which this research is being conducted please contact:

Senior Research Ethics Officer

Bond University Human Research Ethics Committee,

We thank you for taking time to read about this research study.

Yours sincerely,

Professor Tammy Hoffmann **Professor Chris Del Mar** **Dr Mina Bakhit**
Centre for Research in Evidence-Based Practice, Faculty of Health Sciences and Medicine, Bond University

Appendix 3. Patient questionnaire

Researcher use
Study ID:

Patient Questions for nested study

1. How much effort was made to help you understand your health issues?

0	**1**	**2**	**3**	**4**
no effort was made	a little effort was made	some effort was made	a lot of effort was made	every effort was made

2. How much effort was made to listen to the things that matter most to you about your health issues?

0	**1**	**2**	**3**	**4**
no effort was made	a little effort was made	some effort was made	a lot of effort was made	every effort was made

3. How much effort was made to include what matters most to you in choosing what to do next?

0	**1**	**2**	**3**	**4**
no effort was made	a little effort was made	some effort was made	a lot of effort was made	every effort was made

4. After seeing the GP, which option do you prefer? Please check one
   a. ☐ *Using* an antibiotic
   b. ☐ *Not using* an antibiotic

5. Considering the option you prefer, please answer the following questions:

	Yes	**Unsure**	**No**
a. Do you know which options are available to you?	☐	☐	☐
b. Do you know the benefits of each option?	☐	☐	☐
c. Do you know the risks and side effects of each option?	☐	☐	☐
d. Are you clear about which benefits matter the most to you?	☐	☐	☐
e. Are you clear about which risks and side effects matter most to you?	☐	☐	☐
f. Do you have enough support from others to make a choice?	☐	☐	☐
g. Are you choosing without pressure from others?	☐	☐	☐
h. Do you have enough advice to make a choice?	☐	☐	☐
i. Are you clear about the best choice for you?	☐	☐	☐
j. Do you feel sure about what to choose?	☐	☐	☐

6. Below are some things involved in making an informed choice.

Please show how confident you feel in doing these things by circling from 0 to 4 for each item.

I feel confident that I can:

a. Understand the information enough to be able to make a choice	**Not at all confident**	0	1	2	3	4	**Very confident**
b. Ask questions without feeling dumb	**Not at all confident**	0	1	2	3	4	**Very confident**
c. Express my concerns about each choice	**Not at all confident**	0	1	2	3	4	**Very confident**
d. Let the doctor know what's best for me	**Not at all confident**	0	1	2	3	4	**Very confident**

Appendix 4. Systematic review PROSPERO protocol

PROSPERO

International prospective register of systematic reviews

NHS National Institute for Health Research

Does antibiotic use in primary care increase antimicrobial resistance in individuals? A systematic review update

Mina Abdou Thabet Bakhit, John Rathbone, Chris Del Mar, Tammy Hoffmann

Citation

Mina Abdou Thabet Bakhit, John Rathbone, Chris Del Mar, Tammy Hoffmann. Does antibiotic use in primary care increase antimicrobial resistance in individuals? A systematic review update. PROSPERO 2015 CRD42015025499 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42015025499

Review question

To update a systematic review to assess whether bacterial resistance in individuals is caused by prescribed antibiotics in primary care and to strengthen the current evidence base.

Searches

This review is an update for a previous systematic review done by Costelloe et al. (2010). This review will look at studies from May 2009, which was the final inclusion date for Costelloe et al. (2010) systematic review. We will search the clinical trials registers, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE (May 2009 to current date). There are no restrictions in the country, or language of publishing.

We will search the references of retrieved articles and published reviews for additional studies to be included. We will write to authors with significant publications to identify ongoing or unpublished trials. The search will include trials in trial registers such as the World Health Organization's (WHO) clinical trials registry, PROSPERO, and the National Institutes of Health registry of clinical trials.

Types of study to be included

The studies to be in included are randomized controlled trials (individual level or cluster-RCTs) and observational studies (prospective and retrospective cohort or case-control studies) stating quantitative measures of analysis between the prescribed antibiotics and subsequent bacterial resistance.We will exclude studies if they do not measure antibiotics prescribed in primary care or the amount of antimicrobial resistance; not original research, or ecological studies.

Condition or domain being studied

One of the main causes of antimicrobial resistance is its improper use by clinicians in the first point of care. The poor use of various antimicrobials in the treatment of acute respiratory infections, where the benefit is very small, has led to further spread of the resistance.

Despite the spread of resistance among the population and the impact of antibiotics use, clinicians continue to prescribe antibiotics believing that the resistance is caused by factors other than their prescriptions in primary care.

A systematic review by Costelloe et al. (2010) provided strong evidence that antibiotic prescribing in primary care causes resistance in individuals. Resistant bacteria are detectable among commensals as long as 12 months period, although this decays exponentially from a maximum directly after prescribing antibiotics. This result is important information for clinicians and their patients for two reasons: 1) antibiotics cause a threat from resistance to the individual; 2) not using them allows the microbiome to return to antibiotic susceptibility again after about a year. This information might reduce prescribing rates for antibiotics and hence the threat from resistance .

The aim of this review is to update the systematic review by Costelloe et al. (2010) in order to test the current evidence base with more studies.

Participants/population

Types of participants are symptomatic and asymptomatic participants, who are not currently symptomatic, but received a recorded previous treatment with antibiotics, adults and children of both sexes, any age, and without any race or ethnicity restriction.

Intervention(s), exposure(s)

Interventions delivered in any primary care environment and stated quantitative measures of analysis between prescribed antibiotics and subsequent bacterial resistance sampled from any body site, and analysed at the individual level.

Comparator(s)/control

Interventions compared between two types of antibiotics, antibiotics against placebo, antibiotics against no treatment, and antibiotics against non-antibiotic treatments (ex. Steroids, Non-steroidal anti-inflammatory drugs [NSAID]) are to be included.

Context

We will include studies in primary care settings.

Primary outcome(s)

The primary outcome of this review is to assess the strength and duration of any association between the emergence of bacterial resistance and antibiotic prescription in primary care.

Secondary outcome(s)

'None'

Data extraction (selection and coding)

Selection Process:
Search results will be merged into reference management software (Endnote X6) and duplicates will be removed. Results of the searches will be reviewed independently by two review authors. Full text will be obtained if insufficient information was provided in the abstract or no abstract is available. Full text of the potentially eligible articles will be retrieved for full text evaluation. Disagreements will be resolved by consensus and discussions among the review authors. Excluded trials will be identified and listed with the reason for exclusion.
Full articles will be independently reviewed for quality and data extraction. A data extraction form will be developed based on the extraction variables mentioned in the systematic review by Costelloe et al. (2010). A PRISMA flow diagram will be used to report the number of included and excluded studies in each stage of the selection process. The diagram will include the number of studies passed to the next stage in the selection process as well as the number of excluded articles with reasons for exclusion.
Data extraction:
Data from the studies included in the review will be extracted and reported in a tabulated format. The data to be extracted will include details about participant's characteristics; study design; types of prescribed antibiotics; location of recruitment; dose and number of the antibiotic course; time between antibiotic exposure and measurement of resistance; and outcomes important to the review question: location of the sample, type of bacteria, type of antibiotics, method used to measure resistance.

Risk of bias (quality) assessment

The quality of individual studies will be assessed using Costelloe et al. (2010) previously identified quality criteria for studies quantifying the relation between antibiotic prescribing and bacterial resistance. The quality criteria for studies were:
(1) reliable measure of antibiotic exposure;
(2) reliable measure of resistance;
(3) unbiased control selection;
(4) ability to identify incident cases (Patients' bacteria were known to be non-resistant before exposure to antibiotics);
(5) adjustment for key confounders such as recent hospitalization or instrumentation of the urinary tract.

The quality of the study will be rated according to these quality criteria and studies that met fewer than three criteria will be excluded.
Meta-bias(es): we will create a funnel plot to assess the bias. If funnel plot asymmetry exists, we will explore the possible causes.

Strategy for data synthesis

All analysis will be done using IBM SPSS statistics version 22. The outcome measure will be the odds ratio (OR) of resistance in individuals exposed to antibiotics compared with those who were unexposed. The 95% confidence interval (CI) and ORs will be presented by bacterium type, sampling location, and duration between the exposure to antibiotics and time of resistance measurement. We will use I-squared statistic to measure heterogeneity and a random-effects model for any involved meta-analysis.

Analysis of subgroups or subsets

None planned

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21 August 2015

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21 August 2016

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Conflicts of interest

None known

Language

English

Country

Australia

Stage of review

Review_Ongoing

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Anti-Bacterial Agents; Anti-Infective Agents; Drug Resistance, Microbial; Humans; Primary Health Care

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26 August 2015

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26 August 2015

Details of any existing review of the same topic by the same authors
Costelloe, C., Metcalfe, C., Lovering, A., Mant, D., & Hay, A. D. (2010). Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ, 340, c2096. doi: 10.1136/bmj.c2096

Stage of review at time of this submission

Stage	Started	Complete
Preliminary searches	No	Yes
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions
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